# THE SURGICAL CLINICS OF NORTH AMERICA

## UROLOGIC SURGERY

VOLUME 45 – NUMBER 6
DECEMBER, 1965

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# THE SURGICAL CLINICS OF NORTH AMERICA

## UROLOGIC SURGERY

GEORGE T. MELLINGER, M.D., *Guest Editor*

Three-Year Cumulative Index
(1963, 1964 and 1965)

Volume 45 — Number 6

DECEMBER, 1965

**W. B. SAUNDERS COMPANY** — Philadelphia & London

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The following information is published in accordance with the requirements of the United States Postal Code.

The Surgical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey. Subscription price is $18.00 per year. Second-class postage paid at Haddonfield, New Jersey.

This issue is Volume 45, Number 6.

The editor of this publication is Dwight J. Hotchkiss, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 39-19714.

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# SYMPOSIUM ON UROLOGIC SURGERY

## Foreword

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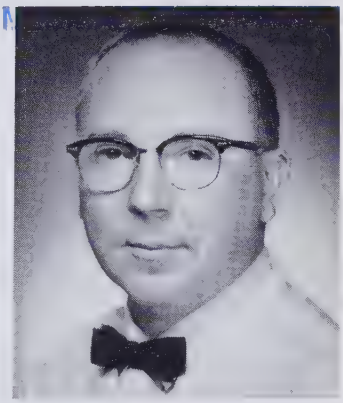

GEORGE T. MELLINGER, M.D.

For many years, the Veterans Administration has supported one of the largest medical complexes, now consisting of 164 hospitals, in the United States. It employs more physicians, nurses, laboratory and auxiliary hospital workers than any other institution. Although these hospitals are entirely devoted to the care of veterans of American wars, the problems encountered by Veterans Administration physicians are not very different from those of other physicians. This is particularly true in the field of urology. Although the urological diseases of the young are not to be minimized, both Veterans Administration and civilian physicians deal with a population which is increasing rapidly in total numbers of older people with the many urological problems accompanying aging. For this reason, Veterans Administration urology has been growing in importance and will continue to grow as the years pass. At the time of this writing there are 104 urology services in the Veterans Hospitals, many of which are operated by full-time urologists, whose staffs are often augmented by private practitioners of urology who serve as consultants.

Shortly after World War II, innovations were made within the Veterans Administration medical network when locations close to medical schools were chosen for construction of new Veterans Administration hospitals. This linked Veterans Administration medicine with the teaching world, making the facilities of each available to both. Thus, many of our Veterans Administration physicians —including the urologists, of course— participate in medical instruction as members of the teaching staffs of medical schools. This especially aids medical schools which depend upon part-time instructors for a portion of their teaching, while also benefiting the Veterans Administration instructor by keeping him intellectually alert

and up-to-date with current developments in medicine in general and in his field in particular. Also, through affiliation of university and Veterans Administration hospitals, wider experience is provided for medical students, residents and staff.

Many of our Veterans Administration doctors engage in extensive research programs, the results of which are available to all physicians. Such contribution to the general advancement of medical knowledge assists in the improvement of patient care, not only for the veteran, but for the non-veteran as well. Thus, the Veterans Administration Cooperative Urological Group is continuing several studies which were begun a few years ago, while other investigations develop as off-shoots of the original program. We hope that these studies, the clinical implications of which are reflected in many of the papers to follow, will yield information of enduring worth to urologists everywhere.

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# Chemotherapy in Urologic Cancer*

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Many patients with urological cancer are beyond the scope of total excision when first seen, or develop local or remote resurgence following initial surgery. The urologist is therapeutically oriented to coping with urological cancer with surgery and/or radiotherapy. In recent years, adjuvant and palliative use of chemotherapy alone and in various combinations with surgery and/or radiotherapy has been introduced.

Considerable progress has been made in the knowledge, analysis and use of cellular physiology as well as the activity of chemotherapeutic agents in the metabolic pathways. Preclinical research has produced more potent, but also more toxic, drugs and newer techniques, but the ultimate goal must be the carefully controlled human therapeutic use. Though it is apparent that none of the drugs has been curative or without objectionable side-effects, the patient with advanced cancer offers a tremendous justification for the hazards of chemotherapy.

## PRELIMINARY CONSIDERATIONS

Basically, any therapy is an experiment in the patient receiving it. Radical extirpative surgical procedures have been developed to combat cancer, with a certain sequential morbidity and mortality. The attendant risks of drug toxicity or surgical complications must be equally acceptable in anticipation of the greater benefit to be derived from the specific therapy. If the therapeutic problem is complex, the physician must exercise his skill and knowledge to the utmost, then finally according to his judgment render the best treatment.

In treating each patient, no matter how complex, confusing or even hopeless his problem, and carefully observing his course, the physician

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* The patients treated by the author are part of a continuing study under the auspices of the Veterans Administration Urological Research Group in Collaboration with the Clinical Branch, Collaborative Research, National Cancer Institute, Public Health Service.

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gains experience and knowledge both in the art of chemotherapy and understanding of cancer. Before initiating chemotherapy, the physician must be familiar with the experimental and clinical application of the various drugs to be used. It is inconceivable that he embark headlong into this field without thorough preparation, just as the surgeon must have the necessary training for complex surgery.

## PROBLEMS IN CHEMOTHERAPY

No cytotoxic drug is specific against malignant cells, and interference is directed against the rapidly dividing cells in normal tissues as well as cancer. Thus, bone marrow and intestinal epithelium are as susceptible as are tumors. This host toxicity curtails the quantity of drug that can be given and may result in incomplete tumor regression. Tumor cells in the same tumor may exhibit varying susceptibility to a drug, with a later resurgence of the poorly responsive tumor or mutant cells into a tumor that will be quite resistant to further therapy with the same or related drugs. In evaluating chemotherapeutic effect, the difference between temporary tumor regression and prolongation of life must be appreciated. The goal is a good palliative result with but limited or controllable toxicity.

Good judgment must be exercised in the choice of patient. Full recommended doses of drugs are given to those patients in a good nutritional state, without extensive hepatic metastases or impaired hepatic function, without previous extensive radiotherapy, with good bone marrow function, without previous intensive use of chemotherapy, and without existing infection. When these factors are unfavorable, one-third or one-half the usual dose should be used. Other considerations are the mode or route of administration, the total amount of the agent to be given over what length of time and to what end-point of toxicity, and the number and frequency of courses of therapy.

Combinations of drugs for synergistic response are used for a therapeutic result which would be greater than if either drug alone was given. To be of value, an increased antitumor effect must be obtained with little additive toxicity for the patient. A combination (either concomitant or sequential) may delay the appearance of drug resistance where the drugs may act at different sites of the same metabolic pathway, or in separate sequences, or in combined fraudulent synthesis or enzyme inhibition. Drug combinations have been evaluated clinically quite intensively in recent years but no exceptionally active combinations have been demonstrated.

Chemotherapy is used alone or as an adjuvant to surgery and/or radiotherapy. As an adjuvant to surgery (with or without radiotherapy), the aim may be to reduce tumor size before operation, prevent recurrence after apparent total tumor removal, reduce cell spread during the surgical maneuvers, treat tumor that could be only partially removed, increase

radiation response, or allow for enhanced host defense mechanism by removal of the bulk of the original tumor.

## CHEMOTHERAPEUTIC AGENTS

The drugs that have shown some usefulness or activity in urological cancer are presented in four classification groups: antimetabolites, alkylating agents, antibiotics and miscellaneous (including estrogens).

### Antimetabolites

Certain analogues of purines, pyrimidines and folic acid displace their structurally similar compounds and interfere with nucleic acid synthesis (1) by inhibiting cell function through enzyme binding, (2) by substitution to produce an abnormal or fraudulent substance, or (3) by interfering competitively with a normal substrate.

6-Mercaptopurine (Purinethol, 6-MP). The major antitumor effect of 6-MP is a direct inhibition of de novo purine nucleotide synthesis by enzymatic blockage at the step from inosinate to adenylsuccinate with a resultant adenylic acid deficiency. Formation of 6-mercaptopurine ribonucleotide constitutes the lethal metabolic synthesis, and resistance to 6-MP results from the loss of enzyme function in resistant cancer cells to form this derivative. Other mechanisms are also concerned in the blockage of cell mitosis. In one catabolic pathway, 6-MP is oxidized to thiouric acid which gives rise to hydrogen sulfide in liver cells, resulting in toxicity. Hepatic toxicity and intestinal ulceration may occur oftener than realized. Before jaundice is evident, an elevated serum glutamic-pyruvic level is an early indication of hepatic damage. Anorexia with tenderness in right hypochondrium or jaundice strongly suggests the necessity of withholding the drug. 6-MP is available in scored 50-mg. tablets and the daily dose orally is 2 mg./kg. or 100 to 150 mg. in adults.

5-Fluorouracil (5FU, FU). After intracellular metabolic conversion to 5-fluorodeoxyuridine, the most detrimental effect of 5-fluorouracil is on the enzyme, thymidylate synthetase, resulting in inhibition of deoxyribonucleic acid (DNA) thymine biosynthesis. In man 5FU is degraded to urea, and it seems that the patients who degrade the drug faster tolerate larger doses. There was more degradation of 5FU given in a continuous infusion than following rapid injection.

Toxic side-effects are seen in the bone marrow and gastrointestinal tract, and, if they are severe, aplasia of the marrow and ulceration and hemorrhage of the gastrointestinal tract occur. The toxicity usually becomes evident after 9 to 14 days of therapy.

5FU is available in 500-mg. ampules and is given intravenously, 15 mg./kg. (not to exceed 1 gram) daily for five days, then 7.5 mg./kg. either daily or every other day to toxicity; an average total dose is 18

grams. The slow infusion of 5FU in 5 per cent glucose solution has been found to be less toxic, but is believed to be less effective in improving objective response.

METHOTREXATE (MTX, Amethopterin). This is the most widely used folic acid antagonist and its predominant anticancer effect is to inhibit folic acid reductase, preventing the conversion of folic acid to tetrahydrofolic acid. Interference with DNA formation by MTX results from inhibition of thymidylic acid synthesis and limits the proliferation of cells by arrest of mitosis. MTX remains bound in tissues where there is a low rate of cell division, typically the liver. Hepatic fibrosis may result from prolonged therapy, especially in the young. Other toxic effects are seen mainly in the gastrointestinal tract and bone marrow.

MTX is available for oral, intramuscular and intravenous use. For children, the daily oral dose is 2.5 to 5 mg., and for adults, 2.5 to 7.5 mg. The drug is given to toxicity, stopped for a few days, and then continued at subtoxic levels.

**Alkylating Agents**

Alkylation can attach an alkyl group to an x-receptor through a sulfur, nitrogen or oxygen atom which reacts through a negative (nucleophilic) center by replacing a hydrogen atom. Evidence suggests that all active alkylating agents have similar cytotoxic mechanism of action and therapeutic activity. They react indiscriminately with many cellular components, but the most important is alkylation of nucleic acids. The potential site of this activity is the hydrogen bonding of the phosphate backbone linkage of the internucleotide helical bodies of DNA, as well as the hydrogen bonding between the helices themselves. The alkylating agents cause changes similar to those found after irradiation, and therefore are called radiomimetic. These changes are: nuclear and cellular disintegration, followed by abnormal mitoses and giant cell formation; bone marrow suppression; epilation; erythema induction; membrane formation; and mutation induction. The effects of cytotoxic drugs are more rapid than in irradiation, probably based on relative effective dose.

CYCLOPHOSPHAMIDE (Cytoxan; Endoxan). Cyclophosphamide functions as a relatively specific inhibitor of cell proliferation with minimal overall toxic effects in bone marrow. Cyclophosphamide is unreactive in vitro, and its inertness may explain its traversing the gastrointestinal tract and blood stream to reach its biological site of activation and reaction. This represents the "carrier" technique, moderating the activity of the mustard by a phosphamide ring. Since the enzyme phosphoramidase is supposed to be high in tumor cells, cyclophosphamide is then supposedly hydrolized into releasing an active cytotoxic compound in these tumor cells.

Leukopenia was the most frequent side-effect but, without it, no antitumor effects were seen. Alopecia was also another frequent toxic sign. Anorexia, nausea and vomiting may be controlled by antiemetic drugs.

Cytoxan is available in 200- and 400-mg. sterile ampules and 50-mg. tablets. Maximum therapeutic effect is obtained initially by intravenous medication up to 30 mg./kg. weekly, and maintenance therapy can be continued orally using 100 to 200 mg. daily, enough to keep the leukocyte count between 2000 and 5000. Children do not tolerate a daily maintenance dose greater than 2.5 mg./kg. When tumor exacerbations occur in spite of the maintenance dose, short courses of intravenous medication within limits of toxic manifestations may be required. The drug may also be given intramuscularly and into body cavities.

Sarcolysin. Sarcolysin and its L-isomer phenylalanine mustard (Melphalan) are examples of substitution of nitrogen mustards with amino acids by synthesizing peptides carrying nitrogen mustards. There is evidence that these compounds enter the amino acid metabolic pathways, but still they seem to act as mustards and not as amino acid antagonists. L-Phenylalanine mustard has been shown to inhibit the incorporation of labeled phenylalanine into nuclear proteins.

Busulfan (Myleran). Myleran was produced by replacing the chlorine atoms of nitrogen mustard with sulfonic ester radicals, resulting in methanesulfonates. Myleran may act by alkylation at the site of the guanine moiety of DNA, thus opening a path for biosynthesis of pteridines, which could then affect hematopoiesis by interference with folic acid. This metabolic pathway could explain the preferential effect of Myleran on granulocytes and granulopoiesis, causing a prolonged period of neutropenia with accompanying depression of platelet and erythrocyte count, but no suppression of lymphocytes.

Lethal pancytopenia has been reported with Myleran as well as prolonged (several months) depression of neutrophils. Diffuse pulmonary fibrosis can occur as a result of Myleran therapy. Jaundice, hepatic coma, altered kidney function and hemorrhagic diathesis have occurred. A syndrome resembling adrenal cortical insufficiency occurred in some patients receiving Myleran over 17 to 72 months of therapy, characterized by skin hyperpigmentation, weakness, fatigue, anorexia, nausea, and weight loss, but without laboratory evidence of adrenal insufficiency. Myleran is available in 2-mg. scored tablets and the daily dose varies from 1 to 5 mg. daily.

Triethylenethiophosphoramide (Thio-TEPA; TSPS). Thio-TEPA is an ethylenimine alkylating agent, and its action is slower than that of other alkylating agents. Its toxicity has been described as mild and it can be given over many months as long as the dose is adjusted to the patient's blood count.

Thio-TEPA inhibits the mitosis of both normal and cancer cells, but reportedly injures nondividing neoplastic cells more than normal cells. There is interference with the functioning of the nucleic acids, inhibition of glycolysis, inhibition of protein and enzyme synthesis, deactivation of

certain enzymes, and cytologic changes. The drug is available as a prepared solution, and is given intravenously, intramuscularly or into body cavities up to 0.4 mg./kg. at one- to four-week intervals, the dosage being adjusted to the resulting toxicity.

CHLORAMBUCIL (Leukeran). Chlorambucil produces chiefly a cytotoxic effect on lymphocytes, and also a suppression of the myeloid and erythroid production of the bone marrow. The drug, in part, acts by a direct effect on nuclear chromatin, and produces the lymphoid effects of radiation. Besides the leukopenia and anemia as side-effects, thrombocytopenia and neurotoxicity may occur. Nausea and anorexia may be related to the size of the dose. Chlorambucil is supplied in 2-mg. tablets, and the dose varies between 0.1 and 0.2 mg./kg. with progressive changes depending on toxicity.

NITROGEN MUSTARD (Methyl-bis[β-chloroethyl]amine). This original alkylating agent reacts with many constituents of both normal and cancerous cells after undergoing a chemical structure change after administration. DNA is most susceptible and the term "polyfunctional" as applied to alkylating agents refers to their mechanism of reacting at two or more points along the DNA complex or by cross linkage. There is an inhibition of mitoses and a production of genetic aberrations. There is a resultant interference with actively proliferating cells with cell mutations and death.

Difficulty in administration is a major drawback of this drug. It must be very carefully administered intravenously with possibilities of thrombophlebitis, and even local slough of tissue if there is any extravasation.

### Antibiotics

ACTINOMYCIN D (Cosmegen). The mechanism of activity of the antibiotics remains in question. It has been postulated that actinomycin D interferes with metabolic pathways dependent on panthothenate, with ammonia assimilation, and with RNA synthesis. Actinomycin inhibits the RNA synthesis coded by DNA by binding to the guanine complexes of the DNA.

The drug is given intravenously, average 15 micrograms per kilogram daily, in courses of five days, repeated as necessary at six-week intervals.

Toxicity manifestations are myelosuppression (especially leukocytes and platelets), gastrointestinal symptoms, and hair loss. These are potentiated by simultaneous radiation therapy. The blood urea nitrogen rises by up to 10 mg. per 100 ml. after each course of therapy, and gradually returns to normal. In children, repeated courses of actinomycin D did not seem to impede normal growth.

### Miscellaneous

DIETHYLSTILBESTROL. The most successful application of chemotherapy to a malignant growth has been in the treatment of carcinoma of the prostate with stilbestrol. The undesirable side-effects of estrogenic

therapy are well known, and the control of the tumor is only partial; eventually in many cases, it escapes from hormonal control. Other synthetic hormones have been tested in an effort to prolong or increase tumor control or to decrease the side-effects. The clinical application of diethylstilbestrol diphosphate (Stilphostrol) and of polyestradiol (Estradurin) may enhance response. Carbestrol (NSC 19962), a nonsteroid estrogenic compound, is currently undergoing a clinical evaluation.

The mode of action of hormones is obscure, but by stimulating RNA messenger synthesis they do have an effect on selective protein synthesis. Estradiol does increase the formation of M-type lactic dehydrogenase (LDH) without changing the H-type LDH levels.

Vinblastine (Velban) and Vincristine (Oncovin). These are indole-indoline alkaloids derived from the periwinkle plant. They are strong metaphase inhibitors and probably act by interfering with glutamic acid metabolism and inhibiting the formation of nucleotides containing adenine and guanine.

Vinblastine is given intravenously into the tubing of a well-functioning intravenous infusion. The usual dosage is 0.3 mg./kg. given weekly. The toxic effects are leukopenia, thrombocytopenia, progressive anemia, reversible alopecia, gastrointestinal dysfunction, and neurotoxicity (diminished deep tendon reflexes, mental depression, convulsions or psychosis).

Vincristine is given intravenously in 150 ml. of normal saline over a period of 60 to 90 minutes. The dose of 0.02 mg./kg. daily for five days, then 0.05 mg./kg. weekly.

Vincristine may cause neurologic aberrations (paresthesias and hyporeflexia, which may progress to sensory and motor deficit), which have limited its use. Hematopoietic depression, constipation and body pains have been observed.

## CLINICAL APPLICATION

When chemotherapy is used, thorough pretreatment evaluation of the patient must be combined with careful progressive clinical and laboratory observation in order to avoid serious toxicity and to observe any beneficial effect. Supportive measures are to be given as indicated.

### Carcinoma of the Prostate

Palliation in disseminated carcinoma of the prostate may be expected to result from diethylstilbestrol and/or orchiectomy in 60 to 80 per cent of patients. Intramuscular injections of polyestradiol phosphate (Estradurin), oral chlorotrianisene (Tace), and subcutaneous pellets of various estrogenic steroid variants have their devoted advocates. Carbestrol, a nonsteroid estrogenic compound, is being subjected to clinical study with some early evidence of promise.

A Veterans Administration cooperative study of therapy in prostatic carcinoma is now well under way and hopefully will eventually answer some of the questions as to the proper therapeutic regimen.

A personal series of 16 patients with far-advanced prostatic carcinoma were given Myleran in a chemotherapeutic screening study, of which 14 were felt to have completed an adequate course of therapy. The drug was not found to have any suppressive or therapeutic value. One patient with penile metastases did have appreciable tumor regression, but only when excessively large escalating doses were given, with a fatal toxicity. One side-effect that was quite evident in a few patients who survived on sequential (carbestrol) therapy was a prolonged neutropenic leukopenia for 6 to 12 months after discontinuing the Myleran.

Seven patients with prostatic carcinoma were personally treated for a minimum of six weeks with oral Cytoxan, of which three were also given oral stilbestrol simultaneously. In none of these patients were the tumor, the symptoms or the clinical course ameliorated.

Vinblastine (vincaleukoblastine, Velban) therapy has resulted in remission in inoperable prostatic rhabdomyosarcoma in children. Neither radiotherapy nor actinomycin D has delayed the rapid downhill progress.

**Carcinoma of the Bladder**

In bladder carcinoma of advanced stage and high grade of malignancy, the five-year survival has been poor no matter what methods of treatment were used. Proper staging, grading and then surgical management with or without radiation modalities are still not carried out uniformly under any given set of parameters.

In inoperable or recurrent advanced bladder cancer, 5-fluorouracil given with concomitant radiation has resulted in complete or partial regression for varying periods of time from 3 to 15 months. The drug is given 15 mg./kg. daily, but not to exceed 1 gram, for five days; then 7.5 mg./kg. daily to toxicity, usually an average of 10 grams total dose, with concomitant irradiation averaging 4000 rads. Tumor regression is often temporary and associated with some degree of toxicity which may be severe. Increased survival time was not necessarily associated with tumor regression and the expected survival in advanced bladder cancer was not apparently prolonged. Combined 5FU and radiotherapy have given encouraging clinical results as adjuvant therapy in total cystectomy and for locally extended carcinoma confined to the pelvis. 5-Fluorouracil is a useful palliative agent, and in those patients who improve, courses of therapy to toxicity have been repeated every 30 days from the last dose of the preceding course.

In a personal series, four patients with bladder carcinoma were treated with 5-fluorouracil. Two obtained no therapeutic effect. One was given two 10-gram courses of the drug seven weeks apart, with progressive metastatic disease and no pain relief. He expired seven weeks after the last course.

The second patient with epidermoid carcinoma of the bladder with extensive pelvic metastases failed to show any improvement during or after a four-week course of combined therapy, using a total of 2600 r and 11.5 grams of 5FU. He expired one month after completing this therapy. Two patients had temporary regression. One patient had developed large inguinal metastases, edema of genitalia and lower extremities and pain, about 2½ years after cystectomy. He received 12 grams of 5FU intravenously in 27 days, and had at least a 50 per cent reduction in the manifestations for three months. Exacerbation was treated then with 1 gram daily for five days, but it had to be discontinued because of severe nausea and diarrhea. Death followed four weeks later. The other patient had been previously treated with partial cystectomy and radon seed implantation into bladder and prostatic metastasis. Excision of bilateral inguinal node metastases was done three years after original bladder surgery, but prostatic metastasis was growing larger, with induration and considerable pain and dysuria. 5FU was given intravenously, 11 grams in 25 days, with subsidence of symptoms and significant regression of the prostatic metastasis during the ensuing two months. The patient then refused to return for further therapy or evaluation, and expired at home six months after the one course of 5FU.

Thio-TEPA, used topically by direct instillation into the bladder, has resulted in varying degrees of regression of bladder carcinoma. This method should be limited to the noninfiltrating papillary well-differentiated tumors (Stage A lesions). The more advanced bladder cancers do not respond significantly. Thio-TEPA 60 mg. in 30 to 60 ml. of water is instilled for two hours at weekly intervals for at least four weeks, or 90 mg. in 100 ml. is instilled on alternate days for four treatments. A transient cystitis may occur, and is partially related to the concentration of the thio-TEPA. After cystoscopic evaluation, the topical course may be repeated or remaining lesions may be fulgurated. Response to therapy is indicated cystoscopically by a disappearance of the lesion, shrinkage, or change from villous papillary tumor fronds to confluent bulbous fronds. Radiation therapy given immediately following several topical thio-TEPA instillations has caused profound bone marrow depression, but in two patients with Stage 2-3 $B_1B_2$ lesions, there were extensive ulceration and sloughing of the tumors. In using thio-TEPA or any topical bladder instillation, dehydration of the patient for 12 hours prior to therapy is of value.

Intratumoral injection of thio-TEPA using a long flexible needle endoscopically has been employed, using 40 to 60 mg. dissolved in 20 to 30 ml. of normal saline. Parenteral injections of thio-TEPA combined with intratumoral injections have resulted in some degree of tumor regression, but have not been considered effective in controlling bladder cancer.

Continuous intra-arterial infusion of 5FU has been employed through an internal iliac catheterization where the 5FU (7.5 mg./kg. in 500 ml. of 5 per cent glucose in water every 24 hours) is given by slow arterial infusion

for five to seven days. Using a percutaneous femoral artery catheterization to the aortic bifurcation and inflated tourniquets around the thighs (20 mm. of mercury above patient's systolic pressure), 5FU (20 mg./kg.) is injected slowly. The tourniquets are left inflated for at least five minutes after the injection is completed.

Methotrexate by continuous intra-arterial infusion through both hypogastric arteries is combined with intramuscular injections of citrovorum factor (6 mg.) every four to six hours. A total of 50 mg. is given daily; 25 mg. of methotrexate in a liter of fluid through each hypogastric artery, until toxicity appears or desired tumor regression occurs.

Embryonal rhabdomyosarcoma including sarcoma botyroides of the bladder is comparatively insensitive to irradiation. If the tumor is inoperable, Cytoxan and vinblastine have been reported to give some degree of regression. In adults, vinblastine is given 10 mg. intravenously at intervals of 4 to 14 days, with a maintenance dose of 10 mg. weekly.

**Renal Cancer**

Chemotherapy in clear cell carcinoma of the kidney ("hypernephroma") has been proposed for inoperable or recurrent metastatic disease, or metastatic lesions after palliative nephrectomy. Cytoxan has given some palliative responses with regression of pulmonary and cerebral metastases, and incisional implants. Hypernephroma has been found not to respond to 5FU, but thio-TEPA has been favorably reported.

In a few patients, actinomycin C has given remission of metastases, and considerably increased survival. Dose is 70 micrograms/kg. daily or 200 micrograms daily. Maintenance therapy is provided with rectal suppositories containing 1000 micrograms, one daily.

In Wilms' tumor (nephroblastoma), the use of actinomycin D has substantially improved the survival rates. The drug may be used preoperatively with radiation in the presence of metastases, or where there is a huge tumor without demonstrable metastases. Six weeks after beginning this therapy, nephrectomy is done, to be followed by another course of actinomycin D. The drug is given intravenously in five daily courses of 15 micrograms/kg.

For inoperable Wilms' tumor, radiation therapy and several courses of actinomycin D have been used. Where pulmonary metastases appear after nephrectomy, or have been present at the time of surgery, radiation therapy is given to the lung fields. Actinomycin D is also given in five-day courses every six weeks for six months, and every three months for up to nine months. For bilateral Wilms' tumor, minimal radiation to both kidneys with a five-day course of actinomycin D, then repeated actinomycin D courses every six weeks for a year, and every three months for the second year. Vincristine has given temporary regression in patients who have become refractory to actinomycin D.

In a personal series, five patients with "hypernephroma" have been treated with Cytoxan. One received insufficient medication to allow evalua-

tion and two others have just recently completed their first course of therapy. One previously nephrectomized patient was placed on constant oral maintenance therapy, surviving 17 months from the time pulmonary metastases were noted. The pulmonary metastases enlarged very little. Manifestations of cerebral metastases (headache, papilledema and projectile vomiting) occurred 9½ months after continuous oral therapy but subsided in a few days after the patient received a supplemental course of intravenous Cytoxan (500 mg. daily for five days). The next cerebral episode with headache, diplopia, vertigo, slurred speech, ataxia of right arm and leg, and vomiting recurred five months later. Intravenous Cytoxan was given, 500 mg. daily for 11 days, with considerable myelosuppression. However, he became asymptomatic and recovered at least 75 per cent of his motor function. Oral therapy (100 mg. daily) was doubled six weeks later when a mild exacerbation of the cerebral symptoms recurred, and again considerable improvement resulted. However, a month later, the fourth cerebral episode was fatal during a convulsive seizure, in spite of a five-day course of intravenous Cytoxan. He had been given a total of 69,200 mg. or 1088 mg./kg. total dose during the 17 months of therapy.

Another nephrectomized patient with pulmonary metastases survived six months on continuous oral Cytoxan therapy (100 mg. daily). He later developed a skin metastasis and incisional tumor implants after ten weeks of therapy, so a supplemental course was given intravenously (400 mg. daily for five days). The skin and incisional deposits regressed by 20 to 50 per cent but the pulmonary metastases steadily increased in size until death. He had received a total dose of 24,300 mg. or 333 mg./kg.

### Adrenocortical Carcinoma

The drug o,p′-DDD(2,2-bis[4-chlorophenyl, 2 chlorophenyl]-1, 1 dichloroethane) has been given orally from 2 to 10 grams daily, the dosage varying according to tolerance. It has a specific cytotoxic effect on all zones of the normal adrenal cortex, the fasciculata and reticularis being more sensitive than the glomerulosa. Nausea, vomiting and diarrhea as side-effects were often controllable with antiemetics; however, somnolence and lethargy usually required that the drug be withdrawn. Prolonged therapy may result in adrenal insufficiency, requiring replacement therapy.

Clinically, there is a marked decrease in urinary steroid excretion, and the metastases (pulmonary, abdominal) usually regress considerably. Resurgence of the tumor, after therapy is discontinued, is marked by recrudescence of the metastases and increased steroid excretion. Resumption of therapy may cause regression, or intermittent therapy may maintain the initial regression for many months.

### Testicular Tumors

Nitrofurazone (Furacin). The use of Furacin has been reported in the therapy of metastatic seminoma and embryonal carcinoma. Various oral dosages were used ranging from 250 mg. to 3 grams daily, with totals

of 30 to 60 grams over periods of 18 to 60 days. Survivals of two to three years have been reported, though peripheral neuritis has occurred and, at times, has forced discontinuance. In an effort to minimize and treat the peripheral neuritis, smaller doses (250 mg. daily) have been given while administering thiamine, parenteral $B_{12}$, and adrenocorticotropic hormones. Nausea and vomiting may limit the size of the daily dose or the length of therapy.

"TRIPLE THERAPY" (Chlorambucil, Methotrexate and Actinomycin D). Triple therapy has given tumor arrest and regression in embryonal carcinoma with metastases. Most of these patients had surgery and/or radiotherapy, or even other chemotherapy. Teratocarcinoma and choriocarcinoma have also responded.

This combination may be given as follows: chlorambucil 8 mg. plus methotrexate 5 mg. daily orally for up to 25 days; plus actinomycin D, 500 micrograms daily intravenously for five-day courses on the third, twelfth and twenty-first days. The courses of treatment may vary from 4 to 28 days, with variation of dosages or interruption of one or the other of the drugs as indicated. Courses will need to be repeated at two- to four-week intervals until evidence of the disease disappears, then at two-month intervals indefinitely. Various series reported objective improvement lasting more than three months in 7 of 13, 8 of 15 and 38 of 55 patients. Tumor regression corresponded to an associated fall in urinary gonadotropin titer. Pulmonary metastases regressed to a greater degree than the retroperitoneal or cervical lymph node metastases.

Reversible toxicity was expressed as stomatitis (probably due to the methotrexate), vomiting and/or diarrhea, and bone marrow depression (leukopenia disturbances of coagulation or anemia).

SARCOLYSIN. In seminoma, the beneficial use of sarcolysin has been extensively reported, especially in the Russian literature. Preoperative decrease in size of the testicular tumor was observed, and in metastatic lesion material obtained at necropsy, dystrophic and necrotic changes were observed. In a series of 42 patients with metastatic lesions after primary orchiectomy (31 patients) or with inoperable primary tumors (11 patients), 21 had good immediate results. The drug was given orally once a week, 30 to 40 mg., and up to a total of 200 to 240 mg. Subsequent four-week courses of 30 mg. weekly were given at four- to six-week intervals, depending on the patient's tolerance and the tumor's response.

In patients responding to sarcolysin, subjective improvement (pain relief, better appetite and overall status) become evident within the first week. Supraclavicular and retroperitoneal lymph node metastases were found more likely to regress than metastases to liver, lung or bone. Responsive tumors did not lose their sensitivity to sarcolysin and recurrent metastases regressed with repeated courses of sarcolysin.

Where lymphogenous metastases had become refractory to irradiation, administration of sarcolysin (20 to 100 mg.) eliminated or decreased this

refractoriness in 32 of 40 patients. Side-effects of sarcolysin, usually minor, included nausea and vomiting, and frequent leukopenia and thrombopenia, but were reversible and well tolerated. Following x-ray therapy, smaller doses of sarcolysin resulted in leukopenia. In a series of 33 patients given sarcolysin, studies of liver function revealed not only that there was no toxic effect on the liver, but that often abnormal values tended toward correction with treatment.

Personal experience with sarcolysin in seminoma has been limited to one patient with extensive metastases. He was given five one-day courses at weekly intervals, 50 mg. per day the first two days, and 40 mg. per day the last three. There was no symptomatic relief, and metastases (hepatic, pulmonary, scapulohumeral) continued to progress until death three weeks after the completion of therapy. As a toxic effect, a severe persistent anemia appeared, requiring 15 blood transfusions in eight weeks.

In presenting sarcolysin, mention should be made of two other bis-(2-chloroethyl) amines, nitrogen mustard and Endoxan (Cytoxan) both of which have caused regression of testicular tumor metastases. Both of these compounds are given intravenously though Cytoxan is relatively much better tolerated and can be given orally in maintenance doses between courses of intravenous administration.

## CONCLUSION

Chemotherapy has proved to be of palliative value in advanced urological cancer, though too often the benefit has been transitory or the drug toxicity prohibitive. Patient survival and tumor regression have not been parallel or consistent.

In spite of the hazards, improved patient morale, better patient care, maximum employment of the physician's skills, and at times an unusually good result are the rewards to those who accept the challenge of using chemotherapy.

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# Considerations of Acute Renal Failure for the Surgeon

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Sufficient progress has been made in understanding the pathogenesis and sequelae of acute renal failure that the present-day surgeon is expected to be familiar with current concepts of prevention, early detection of reversible causes, and the active management by early dialysis of this always serious complication.

## Definition

Acute renal failure is defined as renal function impairment to a degree that biochemical homeostasis cannot be maintained. Its clinical mark is oliguria of less than 400 ml. in 24 hours. Gamble's life-raft studies showed that healthy subjects with maximum renal concentrating ability could excrete an average daily total solute load of 600 mOs in this amount of urine without elevation of the blood nonprotein nitrogen.[8]

The current trend toward thinking of oliguria in terms of urine output per hour rather than per day reflects the need for early recognition of acute renal failure so that corrective therapy may be started before irreversible changes occur. The life-raft study figure of 400 ml. per 24 hours converted to 17 ml. per hour approximates the minimum urine flow presently felt to be required to prevent renal tubular injury, clinically[17] and experimentally,[16] at usual solute loads.

Renal failure needs to be quantitatively differentiated from renal insufficiency wherein homeostasis is grossly maintained by biochemical adjustments, although the kidneys are unable to clear the plasma adequately of metabolic end products. Too often in the postoperative period, surgeons are lulled into a false sense of security regarding renal function because the urine output is greater than 400 ml. per day. Renal insufficiency aggravated by the increased catabolic loads can lead to renal

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failure. This problem is becoming of more concern as the type of acute renal failure with oliguria is seen less frequently.

### Morbidity and Mortality

To appreciate the overall effects that acute renal failure can produce on homeostatic mechanisms, host resistance, and recuperation, the reader is referred to the text on uremia by Schreiner and Maher.[19] Every surgeon must realize that this complication affects all organ systems, and an extensive knowledge of pathophysiology is required if one elects to undertake conservative management of these patients. One may note better tolerance in the young, a difference in the course depending on the underlying disease, or a change in the morbidity with earlier treatment. However, the syndrome is never to be considered benign regardless of how mild the initial insult.

This paper will concern itself primarily with so-called "acute tubular necrosis" which represents about 70 per cent[9] of the cases of acute renal failure and the major problem for the practicing surgeon. The major stimulus for prevention, prophylactic therapy and earlier aggressive treatment lies in the fact that more recent series[21] clearly indicate a reduction of the overall mortality of about 50 per cent and of the high death rate of over 63 per cent of complicated cases reported in earlier large series.[9]

## PREVENTIVE CONSIDERATIONS

A steady decline in the incidence of acute renal failure has paralleled improved care of patients having surgery or other trauma. This decline has occurred independently of the efforts to perfect treatment of the established syndrome. In retrospect, this improvement was heralded by the observations that it was difficult to reproduce the condition in experimental models if a good urine flow was maintained, and that in clinical settings several factors always seemed to contribute to its occurrence.

The surgeon is advised to review the summary article on "The Mechanism of Acute Renal Failure after Injury and Transfusion Reaction and Its Prevention by Solute Diuresis," by Mueller.[14] His documentation of experimental and clinical data strongly suggests that when tubular urine flow is reduced, the kidney is more vulnerable to acute tubular injury by obstruction by precipitates of protein, cellular debris and casts. Conversely, there is increasing evidence that the excretion of urine in adequate quantities protects the kidney in great measure from such intratubular obstruction; and this protective urine flow and dilution may be enhanced, if necessary, by the use of osmotic diuretics such as mannitol.

The pathogenesis of acute tubular necrosis is by no means settled, particularly the role of circulatory dynamics. Ischemia, vasoconstrictive mechanisms, intrarenal shunts, circulating amines, and increased renal

resistance are all possible—but still unproved—primary etiologic injury factors. Evidence presented at the Symposium on Acute Renal Failure held in England in 1964[21] suggested that such factors have not been shown to be of sufficient severity to be the direct cause of organic injury in acute tubular necrosis. For example, direct krypton-85 or xenon-133 gas measurements indicate that renal blood flow is not significantly reduced, contrary to earlier clearance data. There is a reduction of oxygen uptake, but this seems to parallel the decreased activity of a resting tubular state. That the nephron is performing metabolic work is further evidence that this is not an injurious circumstance. Clinicians have long observed that glycosuria, a proximal tubular dysfunction, is not conspicuous with acute tubular necrosis, and at this conference evidence was presented that the ammonium production enzyme system, a more distal function, is intact.

While an altered circulatory dynamics may create a functional disturbance of reduced tubular flow, the precipitation of normally soluble proteins initiating accumulation of mechanical impediments seems the more likely cause of direct damage by obstruction. This could explain the dilatation of tubules, flattening of the epithelium, enlargement of the kidneys and necrotic changes with interstitial leakage of the nephron epithelium resulting from the increased intrarenal pressure contained by a tight renal capsule as observed in experimental rats.[10, 15]

The thesis of tubular obstruction is strengthened by the tagged globin experiments in rats in which this substance—lacking heme pigment—has been demonstrated to precipitate distally in the tubule when flow is reduced by antidiuretic hormone.[14] Recently Patel et al. have demonstrated, as follow-up to experimental studies, that the principal mucoprotein produced by the renal tubule epithelium could be incriminated as causing the renal tubular obstruction in human cases of acute tubular necrosis.[16] With more and more circumstantial clinical evidence that adequate urine flow will prevent or significantly reduce the incidence of the disease, we are nearing a point in medicine where this sequela can more easily be judged as being preventable.

The benefit to be derived from the use of blocking agents to reduce renal resistance and to modify the pattern of cortical to medullary blood flow and/or the transit rate of red blood cells through the kidney is under evaluation. However, from the practical standpoint adequate diuresis must be considered as the best method of protecting the kidneys at present.

## Elective and Semiemergency Procedures

URINARY OUTPUT. The cases of oliguria following cholecystograms call attention to the importance of routinely checking urine output the day prior to operation rather than risk compounding unsuspected renal failure by surgery. Patients are frequently "full of drugs" and this precaution requires emphasis.

Intravenous fluids should be started and an adequate urinary output

demonstrated regularly before administering blood during anesthesia. This point should especially hold for patients submitting to major surgery late in the day, and for older patients who often have some impairment of renal function and who may be especially dehydrated and acidotic as a result of withholding intake since the previous evening.

It is strongly recommended that the anesthetist monitor urine flow from a catheter, this flow being one of the vital signs in complicated major surgical cases.[18] The output should be at least 30 ml. per hour, or about 0.5 ml. per minute, but 60 to 100 ml. per hour is safer to insure the excretion of high solute loads.[2, 14, 18] Solutions with an osmotic concentration greater than 0.3 per cent saline in 5 per cent dextrose and water, started before anesthesia, usually will maintain urinary output even in the presence of antidiuretic hormone effect.[2] Concentrated osmotic diuretics (mannitol 10 to 25 per cent solution) can enhance urine flow quickly without the proportional amount of fluid intake (5 per cent mannitol is isotonic). The checking of urine output should be continued at frequent intervals as one of the vital signs in the postoperative period in complicated cases.

RENAL CIRCULATION. Good preoperative preparation today should include the routine use of blood volume determinations for cases in which extra blood loss is anticipated. An indirect Coombs test should be required when cross-matching blood for patients who have had previous transfusions in order to eliminate the possibility of a hemolytic reaction from a Kell factor. Attention should be paid to plasma deficiencies, as in patients with burns and liver disease.

The concept of a distinct hepatorenal syndrome is disappearing from the literature. Today there is more interest in correcting several factors of liver failure, similar to those which occur with heart failure, which could lead to functional disturbances of the kidney and set the stage for injury.[21, *]

For a time it appeared that the use of osmotic diuretics was not going to be effective in reducing the incidence of acute renal failure following procedures utilizing extracorporeal circulation. Perhaps here was a clinical example in which altered circulatory dynamics did play a direct role in causing organic damage. Yet recent studies indicate that there are several commonly associated etiologic factors, that renal complications are preventable with extracorporeal flow rates greater than 2.2 L./sq.m./min. when perfusions over 30 minutes are anticipated, and that promoting a continuing diuresis is valuable if satisfactory flow rates are not achieved and hemolysis is excessive.[20, 23]

The use of blocking agents such as phenoxybenzamine hydrochloride (Dibenzyline) to counteract circulating pressor amines released during long perfusions or shock is currently under evaluation. When blocking agents such as trimethaphan camsylate (Arfonad) are used in hypotensive anes-

* There is apparently still a question of whether the acute renal failure caused by bunamiodyl (Orabilix) was entirely a nephrotoxic effect.[6] In the 26 cases (2 fatalities) reported, there was a high incidence of associated dehydration and liver failure.

thesia during which the blood pressure is not uncommonly maintained at 80 mm. Hg, extra blood must be given to compensate for the expanded vascular space before there can be a satisfactory urine output.

Every precaution should be taken to prevent endotoxic shock, for in the aged this is becoming the underlying factor carrying the worst prognosis in acute renal failure. Experiments conducted by leading research scientists in this field at a Shock Symposium jointly sponsored by the Civil Aero-Medical Research Institute and the University of Oklahoma Medical Center in November, 1964, demonstrated that none of the current therapies produced a significant beneficial effect from the standpoint of survival. However, there may be a period early in sepsis when aggressive antimicrobial therapy can forestall a hypotensive episode.

Acidosis. Acidosis can cause decreased renal blood flow by carbon dioxide retention and by products of anaerobic metabolism.[4] Treatment with mechanical pulmonary aids and the use of extracellular buffers ($NaHCO_3^-$) can modify its effects, but earlier detection of acidosis is needed. This should be facilitated with the availability of blood pH, $pCO_2$, and $HCO^3$ determinations utilizing simplified portable apparatus, which hopefully will be part of the diagnostic armamentarium of hospitals before long.

Acidosis may be aggravated acutely by anesthesia and by poor tissue perfusion. Some anesthetists knowledgeable of the narrow margin of safety of intracellular buffer agents can skillfully use TRIS (hydroxymethyl aminomethane; THAM) to combat acute acidosis dramatically and in addition achieve a diuretic effect.[4, 12] Under these circumstances, as with mannitol therapy, it must be remembered that a good output does not necessarily reflect good functional status of the kidneys.

When tissue perfusion is poor and acidosis is accelerated, it is debatable whether a vasopressor or a vasodilator drug is indicated. It is probable (although this has not been fully demonstrated) that the lower pH of the filtrate present in acidosis may contribute to the precipitation of proteins in the tubules under circumstances of low flow or hyperosmolality. From the renal standpoint, then, measures to increase urine flow are favored over temporarily increasing tissue perfusion.

Excess Circulating Substances. Occasionally acute renal failure is associated with hyperuricemia following radiation or chemotherapy of malignancies, with hyperproteinemia or dysproteinemia as in multiple myeloma, or with the hypercalcemia of hyperparathyroidism or sarcomas, etc. This complication has been precipitated in such states by diagnostic studies such as urography. It may be that these are simply additional examples of another solubility factor making the kidney more vulnerable to injury under low urine flow. In states of excess circulating substances, strict attention should be paid to urine output, for diagnostic procedures can probably be undertaken safely if urine output is enhanced by the use of osmotic diuretics.

### Emergency or Special Procedures

Several clinical situations seem to demand a prompt and ample diuresis to protect the kidney and standard fluid therapy should be augmented with osmotic diuretics such as mannitol. The first of these is the case of acute trauma in which crushing of tissue may release excessive amounts of protein, pressor amines and acid metabolites. Here diuretic therapy should have priority as soon as the acute resuscitative measures for airway and circulation have been met.

Many surgeons believe a second indication occurs whenever the renal artery is occluded temporarily, as for example during partial nephrectomy, nephrolithotomy for staghorn calculi, or renovascular procedures including kidney transplantation.

Third, many agree that such prophylaxis is advisable in situations in which there may be a more direct reflex reduction of renal blood flow by constriction of renal vasculature, as may occur when the aorta is cross-clamped below the renal arteries, or with aortography.*

## RECOGNITION AND TREATMENT OF REVERSIBLE CAUSES

The second major point to be emphasized is that the organic or irreversible state of acute renal failure may be preceded by a functional or reversible stage.[1] It is therefore most urgent that the surgeon recognize oliguria early and institute prompt prophylactic measures.

### Prerenal Causes

Prerenal factors resulting in impaired circulation to the kidney are the most common cause of oliguria and often are suggested at the first examination of the patient. Some valuable clinical clues are syncope upon elevation of the patient's head, longitudinal furrowing of the tongue indicating advanced dehydration, "warm" shock, and central venous pressure measurements. Obvious deficits of blood, water and salt should be made up and experience has shown that, if the circulatory insufficiency is remedied within four hours, there will be a gratifying urine output and subsequent renal damage will be avoided. With the effectiveness of osmotic diuresis established, however, the possibility of renal injury in many cases should not be chanced, and mannitol may be both diagnostic as well as therapeutic when used early and concomitantly with other fluid therapy. A positive response manifested by a urine output of 100 to 200 ml. within one to three hours usually starts within 30 minutes following the intravenous syringe injection of 50 to 100 ml. of 25 per cent mannitol solution.

* In both of these procedures other factors may also play a role. "Mannitolization" has been considered earlier for extracorporeal circulation, especially when perfusion is prolonged.

This holds true unless the patient remains markedly hypotensive (less than 60 mm. Hg) or dehydration is severe. If the response is favorable, therapy is continued with a 10 per cent solution of mannitol until the prerenal deficit is corrected and the patient is maintaining an output of 100 ml. per hour, or a limit of 100 grams each 24 hours is reached. A tendency to over-replace fluids in the early diuretic period is justified to keep the tubules dilated and flushed, but this action must be carefully monitored preferably by central venous pressures or continuous weighing. Prolonged use of hypertonic mannitol solutions is not advised for they tend to dehydrate the patient. Further, saline needs to be administered or used as a carrier solution as some sodium is lost with forced diuresis.

If there is no immediate output, the test dose of mannitol should be limited to 25 grams in a 25 per cent solution or to 50 grams in a 10 per cent solution. Mannitol—unlike urea—does not migrate into cells and therefore attracts water both from within cells and the extracellular space, and cardiac failure could occur with excessive hypertonic doses.

Confirmatory tests for acute renal failure are findings of similar osmolality between serum and urine, a relatively high urine sodium (often over 100 mEq./L.), or special cells and casts in the urine. Dextran compounds produce high urine osmolality and specific gravity readings, which may falsely suggest dehydration and good renal concentrating ability.

Evidence in humans suggests that the reversible period for renal failure may be as long as 60 hours.[18] The question that there may be a time limit for the administration of an osmotic diuretic after the appearance of oliguria is as yet unresolved. The author's experiments showed that delay in administering mannitol for more than two hours after pigment injection in a few rats produced more obstructed kidneys than it did in control animals given the same dose of pigment without mannitol,[15] and Mason noted a case of oliguria which proceeded to anuria when mannitol therapy was delayed, and exceedingly large kidneys were found at postmortem study.[11] At present, with so many variables in the clinical situations and with little contradictory evidence, cautious trials with mannitol seem appropriate at any time.

**Postrenal Obstruction**

Suspicion of postrenal obstruction is usually aroused by anuria rather than oliguria, and the differential diagnoses include acute glomerulonephritis, a major renal vascular occlusion, and cortical necrosis. The last is more often associated with toxemia of pregnancy or a concealed hemorrhage of the uterus. The radioactive renogram is a valuable, quick and innocuous technique for diagnosing such obstruction. It can be done with postoperative patients in bed and has proved so reliable in ruling out acute obstruction that confirmation by instrumentation is probably unnecessary. If this method is not available, cystoscopy with insertion of ureteral catheters is indicated in an anuric patient, particularly if there is a question

of renovascular occlusion. Often there is no urgency to relieve suspected postrenal obstruction in the first 24 hours unless infection is present. Therefore, a constant drip urogram, or a standard urogram with delayed films up to 18 hours may be used which disclose the obstruction and its exact location more often than is generally appreciated. In certain clinical situations, these have distinct advantages over retrograde catheterization. For example, in cases of advanced malignancies one may not want to relieve the obstruction temporarily only to be forced later to do a high urinary diversion procedure to control the infection that inevitably accompanies prolonged insertion of foreign bodies. Bilateral nonopaque calculi are sometimes not only better located by dye excretion, but also retrograde studies may cause edema which will delay spontaneous passage of the stones.

Acute renal failure following retrograde urological procedures is rare today. Few studies are performed on patients with severe uremia. Small nonobstructing catheters are used for routine pyelograms so that any excess pressure of dye injection escapes alongside these and is not transmitted directly into the kidney. When obstructing catheters are used, as for split renal function studies, a hypertonic osmotic diuretic is usually administered to produce a higher gradient of urine flow to stimulate peristalsis of the tract and to possibly reduce ureteral edema.

**Renal Causes**

Osmotic diuretics will enhance the elimination of exogenous poisons or excesses of endogenous breakdown products such as uric acid.[5] To protect the kidney, this therapy should be tried even if preparations are under way for immediate dialysis. As an example, the value of the prompt recognition and treatment of a severe hemolytic reaction is offered.

Several years ago, an elderly patient received 2 units of mismatched blood during prostatectomy. Diffuse bleeding from all surfaces signaled the diagnosis. The patient was immediately given 8 per cent urea until mannitol, which was not then readily available, could be secured. The patient developed transient oliguria, and jaundice, but diuresis was rapid and he recovered. There is no control case for direct comparison, but judging by clinical experience, this prompt recovery would be unexpected without immediate therapy.

Exploration for acute renal artery occlusion is a newer procedure for reversing a cause of renal failure. In the past, several hours usually had elapsed until a diagnosis was made and it was presumed that infarction had occurred which by definition was irreversible. There seemed little point to perform major surgery for a solitary afflicted kidney or to remove one of two kidneys that would atrophy and not be a source for hypertension or infection. Now it has been shown that the integrity of renal tissue is preserved at surprisingly low blood flows and at pressures of only 25 mm. Hg during which no significant amount of urine is formed.[13] More recently a

very few clinical cases have confirmed that renal function may be restored after renal artery embolectomy following up to four days of anuria.[3] Emboli to the renal vessels are relatively rare, but such reports should encourage us to be alert for this now more favorable diagnosis. While there may be local vasoconstriction immediately, later aortograms or renograms indicate that the occlusions are apparently not complete.

Patients having anuria because of glomerulonephritis or cortical necrosis have generally not increased their urine output immediately with any specific therapy including osmotic diuretics.

## TREATMENT CONSIDERATIONS

The greatest incidence of acute tubular necrosis, a term which Mueller has reintroduced as representing predominantly "lower nephron" pathology,[14] still occurs in association with surgery and trauma. Such cases usually are complicated as a result of increased catabolic states and will require skilled management to reduce their prevailingly high morbidity and mortality. The treatment of acute renal failure should become a standard part of postoperative surgical care including a knowledge of the guidelines for dialysis, methods of fashioning arteriovenous shunts, and the placement of peritoneal cannulae.

Underlying Disease. The increasingly successful management of acute renal failure now requires a first obligation to treat aggressively any underlying disease, which today has become the principal cause of death. A diagnosis of acute renal failure is no longer a contraindication to needed diagnostic and therapeutic procedures. There should be no more hesitation to close a perforated viscus, to reoperate for hemorrhage or to remove a septic uterus any more than to dialyze immediately in cases of poisoning. One should not "wait until the patient is better" to debride or to drain any source of continuing contamination.

Delay of Treatment or Referral. Delay of adequate therapy presently accounts for the second major cause of morbidity and mortality. While renal centers are beginning to report increased survivorship in patients having extreme catabolic states, utilizing earlier and more frequent and physiologic dialysis,[21] still a high percentage of patients require dialysis within 12 hours of transfer (40 per cent) and have a high death rate within 24 hours (15 per cent) strongly suggesting a factor in delay of referral.[9] There are also indications that deaths and secondary complications of less severe renal insult and underlying disease are disproportionately high and might be prevented by alert supervision and perhaps earlier dialysis.

The availability of peritoneal and extracorporeal dialysis using disposable supplies and prepared solutions will make it possible to treat this complication better at community hospitals. Nevertheless, the optimal care of these patients ultimately depends on skilled management, and if a

surgeon is not equipped to render this kind of care or is unable to obtain adequate consultation, the present mortality figures demand that he refer such a patient to a renal center.

SECONDARY COMPLICATIONS OF UREMIA. Uremic complications are the third major cause of mortality. As a consequence of the general improvement in the conservative management of acute renal failure, a shift has occurred over the years in their pattern. Deaths from hyperkalemia and the administration of excessive amounts of fluid early in the course have changed to deaths principally from infection, gastrointestinal hemorrhage or respiratory failure later in treatment. This period of experience pointed the way to taking precautions, by isolation, against introducing outside infection; minimizing the use of foreign bodies such as catheters, intestinal tubes, and long-indwelling venous cannulae; maintaining oral feedings; and improving pulmonary hygiene by ambulation and mechanical aids. A relatively high mortality of 50 per cent persisted, however, despite the adjunct of dialysis, and eventually the concept of early and repeated dialysis evolved.[22]

## GUIDELINES FOR CURRENT MANAGEMENT

More attention is being directed today to making the patient comfortable and to controlling the uremia than adhering to the extremes of a strict conservative or a daily dialysis program. A strong distinction, however, should be recognized between those complicated cases in which there is more rapid catabolism and acidosis associated with trauma, surgery, sepsis and shock, and the more benign instances such as those following a mismatched transfusion and poisonings in which tissue breakdown is relatively smaller and slower to occur.

If it is obvious by the severity of the underlying disease that there will be rapid accumulation of tissue breakdown products, then a preliminary shunt should be placed immediately and preparations made for dialysis at any time. These patients must be observed several times a day. The course of uremia generally follows the blood urea nitrogen and any patient showing a rise in this value of at least 25 to 30 mg. per 100 ml. per day presents a strong indication for the need of early and repeated dialysis.[21]

Even though the uncomplicated cases in general are more amenable to a longer period of treatment without dialysis, it is wise to bear in mind that the renal insult may be severe. Also, an underlying problem such as cardiac or liver failure may be such an aggravation that the recovery period is longer than that of the average complicated case. Suggested criteria for dialysis are a rise in blood urea nitrogen to 100 to 150 mg. per 100 ml. -the lower figure for older patients[21]—a blood phosphorus of 9 to 10 mg. per 100 ml.,[7] or a week of oliguria. Clinical indications for dialysis are present when the uremic patient can no longer tolerate oral intake,

remain ambulatory, or be comfortable—situations which may occur before the above blood chemistry levels are reached.

Another consideration for advocating earlier dialysis is the prevention of a complication of dialysis itself—the so-called disequilibrium syndrome.[21] Particularly with patients having high levels of azotemia and using fast flow artificial kidney machines, a gradient appears between the concentrations of plasma and cerebral spinal fluid solutes. This so-called "blood-brain barrier" is greater with a substance like urea, which is readily dialyzed, and much less with substances like phosphorus and bicarbonate, which are only slowly dialyzed. A similar phenomenon apparently occurs between the plasma and muscle cells and the plasma and red blood cells. All these may result in clinical disturbances such as sensorium changes, convulsions, cardiac irregularities, hemolysis, or hyperventilation, and all contribute to morbidity and mortality. Most of the nonprotein nitrogen residue of dialyzed fluid has been identified and to date no specific toxic substance peculiar to uremia only has been found.[21] The disequilibrium syndrome can be prevented by loading the dialysis bath with urea or a higher concentration of glucose, or by intermittently administering intravenous mannitol.[21] The best measure of prevention is to dialyze early. Better techniques depending upon one's facilities are to use slow flow units, short dialyses on fast flow units at more frequent intervals, or peritoneal dialysis. The latter may be a suitable route at times even after abdominal surgery.

## THE PROBLEM OF RENAL INSUFFICIENCY

The final consideration of renal failure to be stressed is the subtle but dangerous problem of renal insufficiency. Pre-existing renal impairment becomes aggravated by various circumstances that can attend surgical procedures. Too frequently at morbidity-mortality conferences, cases are presented describing a postoperative rise of blood urea nitrogen and a sequence of complications such as delayed wound healing with dehiscence, increased susceptibility to infection, and not infrequently death due to respiratory failure. In retrospect, serious thoughts of aggressively treating these possibly uremic manifestations were not entertained, generally because the patient was putting out a usual amount of urine. One cannot help but wonder, as a result of experience with earlier and repeated dialysis in acute renal failure, whether the course of these patients might have been altered by better control of the uremia. Our medical colleagues are trying dialysis to ease burdens of chronic cardiac and liver failure in selected patients; the prognosis should be even better in surgical patients recuperating from a temporary underlying problem. With this in mind, careful evaluation of renal function before major surgery, the preoperative dialysis of azotemic patients, and the placement of shunts or a peritoneal cannula at operation for postoperative dialysis should be encouraged.

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# The Diagnosis of Renal Cyst Versus Renal Carcinoma

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Prior to the advent of aortography and nephrotomography, the diagnosis of a space-occupying mass of the kidney was the indication for surgical exploration. Although several reports recommended percutaneous lumbar puncture of the mass as a method of differential diagnosis between a cyst and carcinoma, this was not generally adopted. The intravenous pyelogram, retrograde pyelography, perinephric air insufflation, associated with a careful history and physical examination adequately revealed the presence of a renal tumor. The question whether this lesion was a benign cyst or a malignant mass did not pose a problem with respect to surgical intervention since roentgenographic differential diagnosis had not reached that epitome of accuracy which is claimed at the present time. The introduction of aortography and nephrotomography has reduced the erroneous diagnosis to a level between 5 and 10 per cent. When supplemented by translumbar percutaneous aspiration and injection of a contrast medium into the renal mass the degree of diagnostic error may be lowered to 2 per cent.

In spite of all these radiographic technical advances, case reports continue to appear in the literature describing the coexistence of cysts and carcinoma in the same kidney as well as errors in diagnosis discovered at operation after nephrotomography and aortography. One cannot help but suspect, since these reports are not infrequent, that the modern techniques of diagnosis may not yet be so indisputably infallible that one can confidently state that surgical intervention should be deferred.

The present discussion limits itself to the differential diagnosis between renal cyst and malignant tumor and their treatment, since these comprise the most commonly found space-occupying lesions of the kidney.

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Under cysts, one must consider the simple, multiple and multilocular cysts, as well as polycystic renal disease. Advanced hydronephrosis can simulate a renal cyst but will not be discussed at this time. The malignant tumors are the renal cell carcinoma, the cystadenocarcinoma which frequently undergoes cystic degeneration, and the pelvic transitional cell carcinoma.

## CLINICAL AND LABORATORY DIAGNOSIS

SYMPTOMS. In describing the symptoms characteristic of the cyst or carcinoma it is significant that the complaints are common to both, but differ only in degree. Gross hematuria is found in both lesions but occurs in 40 per cent of malignant tumors and in 13 per cent of cysts.

Pain, when associated with a malignancy, is usually colicky due to the passage of blood clots, but can be dull aching in character. It occurs in 22 to 30 per cent of cases. The cystic tumor causes local distress, referred to as a dull dragging ache, due to the weight of the enlarged cyst.

Weight loss can be found with both cyst and carcinoma. Although more common in the malignant tumor, gastrointestinal distress due to displacement and pressure by the enlarged renal cyst can result in weight loss.

Pyrexia has been noted in 18 to 20 per cent of all renal tumors but an infected renal cyst, although infrequent, can produce the same febrile response.

Hypertension has been found in both carcinoma and cyst. There have been occasional reports of elevated blood pressure returning to normal following nephrectomy or excision of a renal cyst. However it is believed that this incidence, 2 to 3 per cent, is equal to the incidence of hypertension in the general population. In polycystic renal disease, hypertension is a common finding.

PHYSICAL AND LABORATORY EXAMINATIONS. The physical examination usually reveals a nontender palpable mass which moves with respiration. Palpation of this mass does not lend itself to a differential diagnosis. The abnormal laboratory finding of anemia is common to both cyst and neoplasm but is encountered more frequently in carcinoma. Polycythemia is found in 4.4 per cent of all renal malignancies and in 2.6 per cent of all cysts. Murphy et al. considered that the pressure of the tumor or cyst on the renal tissue initiates the release of erythropoietin, while Cohen suggests that the oxygen supply and demand relationship, which is altered by the presence of a large mass, releases the hemopoietic factor, causing polycythemia.

Owing to the lack of capable cytologists, the differential diagnosis of renal cyst and neoplasm by exfoliative cytological examination of the urine has not been generally utilized. Cytology requires an extremely careful and exact study in which only a few are proficient. Moreover, it

has been noted that renal parenchymal tumors exfoliate into the tubules at a late stage and as a result cytology has been relegated to a secondary position. The early reports which claimed that elevated urinary lactic dehydrogenase isoenzymes were specific for renal carcinoma were found inaccurate, since more recent studies revealed the enzymes to be significantly elevated in cysts and inflammatory disease of the urinary tract. Thus the clinical symptoms, laboratory studies, history and physical examination do not contribute any distinguishing features toward the differentiation between renal carcinoma and cyst.

## RADIOGRAPHIC DIAGNOSIS

It is in the area of radiology where the new technical modalities have shown their greatest strides in diagnostic proficiency of the renal mass.

### Intravenous Urography and Retrograde Pyelography

The presence of a renal tumor is confirmed by intravenous urography or retrograde pyelography. The kidney is enlarged and its soft tissue contour may be disfigured by a bulging outline. The contrast media can reveal distortion of the calyceal structure by compression, obliteration, displacement, elongation of the infundibuli, or filling defects within the calyces. Calcification may be present and the longitudinal axis of the kidney can be altered by an enlarging mass. The distorted appearance of the calyceal system indicates only the presence of a tumor and at this stage one can, in about 70 per cent of the cases, differentiate between a carcinoma and cyst. Calcific densities within the confines of the renal shadow on the preliminary film are associated in 3 per cent of the cases with renal cysts but appear in 14 per cent of the neoplastic tumors. The calcific deposits are visualized as scattered particles, curved linear opacifications, or as a calcified ring. The latter should not be confused with the calcified hydatid cyst.

The renal cyst is usually located at either pole and the superior or inferior calyx is compressed and displaced toward the midrenal area, forming a smooth crescentric outline. The polar area presents a rounded opacity which is less dense than the bordering renal shadow. The renal polar cyst, as it slowly enlarges, seeks the path of least resistance, extending its growth away from the kidney and permitting the other calyces to maintain a normal pattern. When the cyst is centrally located, the calyces appear to be separated by a smooth round mass and tend to promote a circular contour around the mass. Multiple cysts distort the internal structures and demonstrate a bizarre outline of the calyces, making the diagnosis very difficult. Polycystic renal disease is more easily diagnosed since both renal shadows are abnormally enlarged and the calyceal structures are elongated and displaced.

The renal cell carcinoma obliterates and distorts the calyces and may appear more dense than the surrounding kidney. When the malignant tumor is located at the polar ends of the kidney it dictates an inward or central expansion, replacing the parenchyma and enlarging the renal shadow in its destructive course. Thus one may find all the calyceal structures involved by the neoplastic process.

### Translumbar Percutaneus Aspiration Plus Radiography

Although the diagnosis of a renal mass was an indication for surgical intervention, Fish and Dean recommended percutaneous translumbar puncture of selected kidney tumors when a benign cyst was suspected. Aspiration of clear amber fluid with absence of malignant cells on cytology examination, and the appearance of a smooth circular outline when contrast media was injected into the mass, confirmed the diagnosis of a benign renal cyst. A renal cell carcinoma was suspected when hemorrhagic fluid was obtained on aspiration or an irregular opaque outline was visualized on injection of the contrast media. Although this modality had its enthusiastic supporters, statistics indicated that 3 to 5 per cent of all clear fluid cysts and 25 to 30 per cent of all hemorrhagic cysts were associated with carcinoma.

The percutaneous diagnostic approach was received with some apprehension because of several hazardous features. Chief among these was the question of perinephric spillage of malignant cells from the needle puncture and along the needle tract. Puncture of the liver, spleen and bowel was possible, and the complications of hemorrhage from the kidney as well as the introduction of infection into the cyst were not to be minimized. Small intrarenal cysts were difficult to locate and confusion could arise in cases in which associated pancreatic, mesentric or ovarian cysts were present.

### Coexistent Cyst and Malignant Tumor

Gibson reviewed the various relationships between cyst and carcinoma existing in the same kidney and suggested four possibilities. First the cyst and malignant tumor could arise as separate lesions in two distant regions of the kidney, each maintaining its own identity.

CASE I. D.J., a 65 year old white man, was admitted in November, 1957 complaining of gross hematuria associated with back pain of 1 week's duration. A suprapubic prostatectomy and cystolithotomy had been performed at another hospital 2 years ago. The laboratory findings revealed a hemoglobin of 12.5 gm. and a white blood cell count of 15,350 with a normal differential. The urine showed gross blood and 4+ albumin. The intravenous urogram and retrograde pyelography suggested a neoplasm of the lower pole encroaching on the renal pelvis (Fig. 1, *A*). Exploratory surgery revealed a large parapelvic cyst which contained clear amber fluid, and on the posterolateral aspect of the lower pole an irregular bulging tumor mass was present (Fig. 1, *B*). The pathology report was papillary cystadenocarcinoma. Gross examination of the specimen demonstrated that the area showing distortion, displacement and filling defect on pyelography was actually a benign

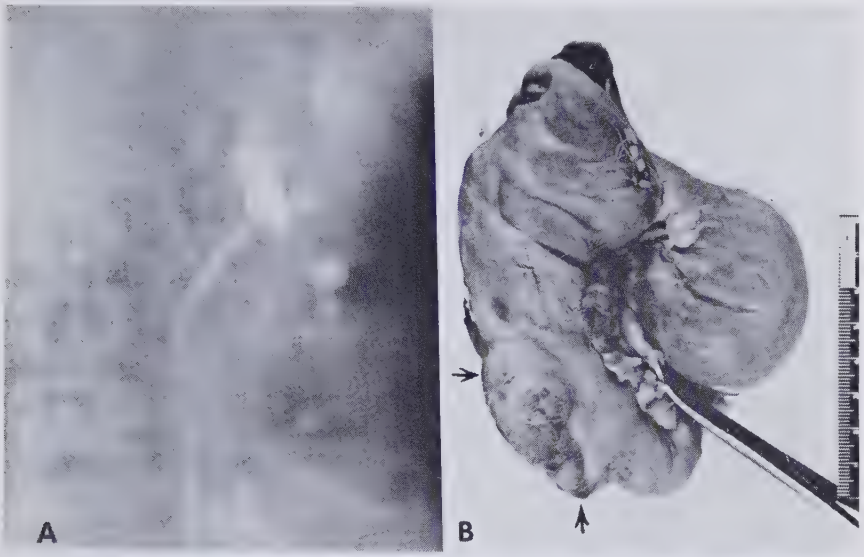


Figure 1. *A*, Retrograde pyelography demonstrates a space-occupying mass causing distortion and filling defects of the inferior calyces, pelvis and upper ureter. *B*, The posterior vein reveals a parapelvic cyst located anterior to the renal pelvis and arrows delineate the neoplasm on the inferior posterolateral surface.

cyst, while the malignant tumor, located on the lateral aspect, did not disturb the calyceal structure and was missed on the radiographic study.

*Comment.* This illustrates an error in diagnosis as well as the possibility of two lesions arising in the same kidney at two distinct separate foci.

Secondly, cystic degeneration of the central core of a large malignant tumor is a frequent manifestation. Blood vessel destruction by the peripheral neoplastic process can produce central necrosis and liquefaction. The papillary cystadenocarcinoma of the kidney usually has a large cystic area.

CASE II. D.D., a 78 year old white man, was admitted to the medical service complaining of right lower abdominal pain associated with nausea and vomiting of 2 weeks' duration. A weight loss of 15 pounds in 3 months was admitted but urinary symptoms were denied. The hemogram was not remarkable and the blood urea nitrogen was normal. Microscopic hematuria was found. The cardiac work-up revealed arterioscletoric heart disease with fibrillation and radiography of the colon showed diverticulosis. Palpation of the obese abdomen was inconclusive for a mass. Intravenous urography and retrograde pyelography demonstrated a superior pole mass displacing the renal pelvis downward and obliterating the superior calyx, thus favoring the diagnosis of a renal cyst (Fig. 2, *A*). Since the patient was considered a poor surgical risk, translumbar percutaneous aspiration was performed and 80 ml. of a thick chocolate-colored fluid loaded with cholesterol crystals was removed. This was replaced by 50 ml. of a contrast media. The roentgenograms visualized a round mass with an irregular contour of the inferior medial aspect (Fig. 2, *B*). Cytology of the aspirated fluid showed old blood. Operative intervention revealed

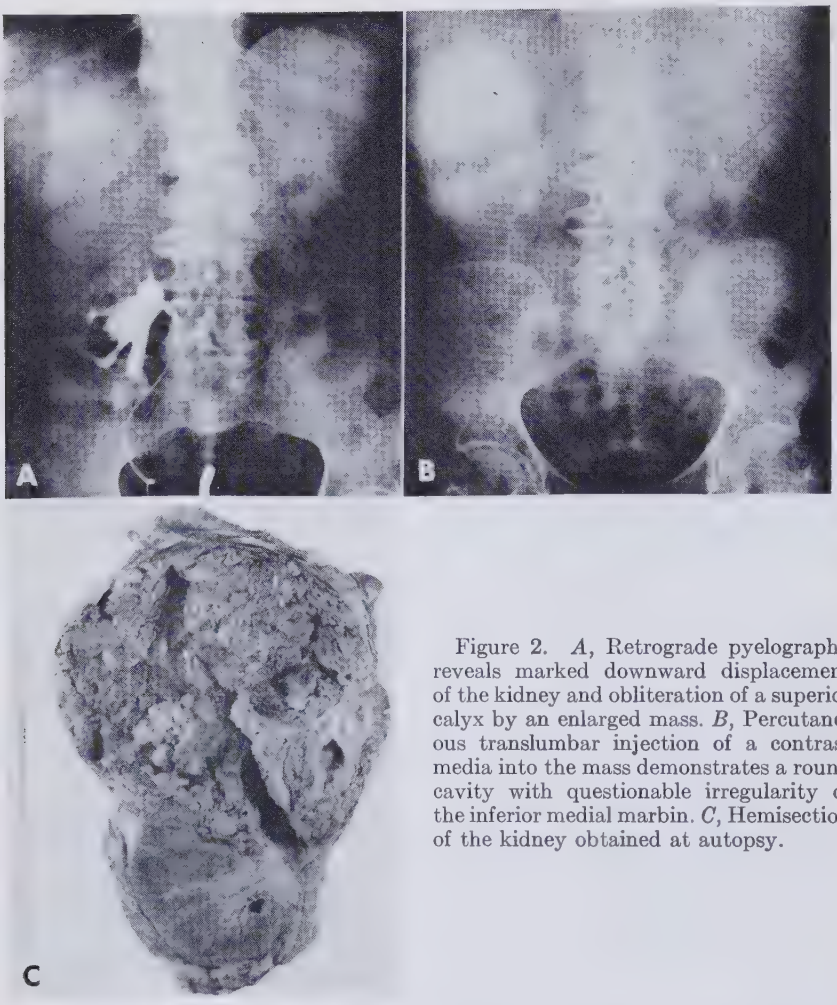


Figure 2. *A*, Retrograde pyelography reveals marked downward displacement of the kidney and obliteration of a superior calyx by an enlarged mass. *B*, Percutaneous translumbar injection of a contrast media into the mass demonstrates a round cavity with questionable irregularity of the inferior medial marbin. *C*, Hemisection of the kidney obtained at autopsy.

a large, fixed, inoperable tumor mass with extensive involvement of the para-aortic lymph nodes. The renal biopsy was reported as papillary cystadenocarcinoma. The patient expired 8 months later (Fig. 2, *C*).

*Comment.* The percutaneous introduction of a contrast media into the tumor mass revealed an extensive central necrosis which was circular and difficult to differentiate from a cyst. The hemorrhagic aspirate made exploratory surgery mandatory.

As a third possibility, a carcinoma may arise on a cyst wall. This tumor is located within the cyst cavity on one area of the membranous lining. Individual case reports of this rare association appear sporadically in the literature.

The last category of coexistence of carcinoma and cyst is based on

Hepler's theory of cyst formation, namely, that renal tubular obstruction associated with local vascular disturbance will create a cyst in that sector. A malignant mass can obstruct tubular outflow and simultaneously compress or cause thrombosis of the local blood supply, fulfilling the fundamental requirements leading to cyst formation distal to the tumor mass. Examination of this specimen reveals a neoplasm intimately adjacent to a clear cyst, but separated from one another by a thin membrane, usually the cyst wall.

CASE III. J.H.K., a 68 year old white man with paraplegia secondary to arachnoiditis since 1959, was admitted to the physical medicine service in November, 1964 because of a sacral decubitus. A routine intravenous urogram suggested a

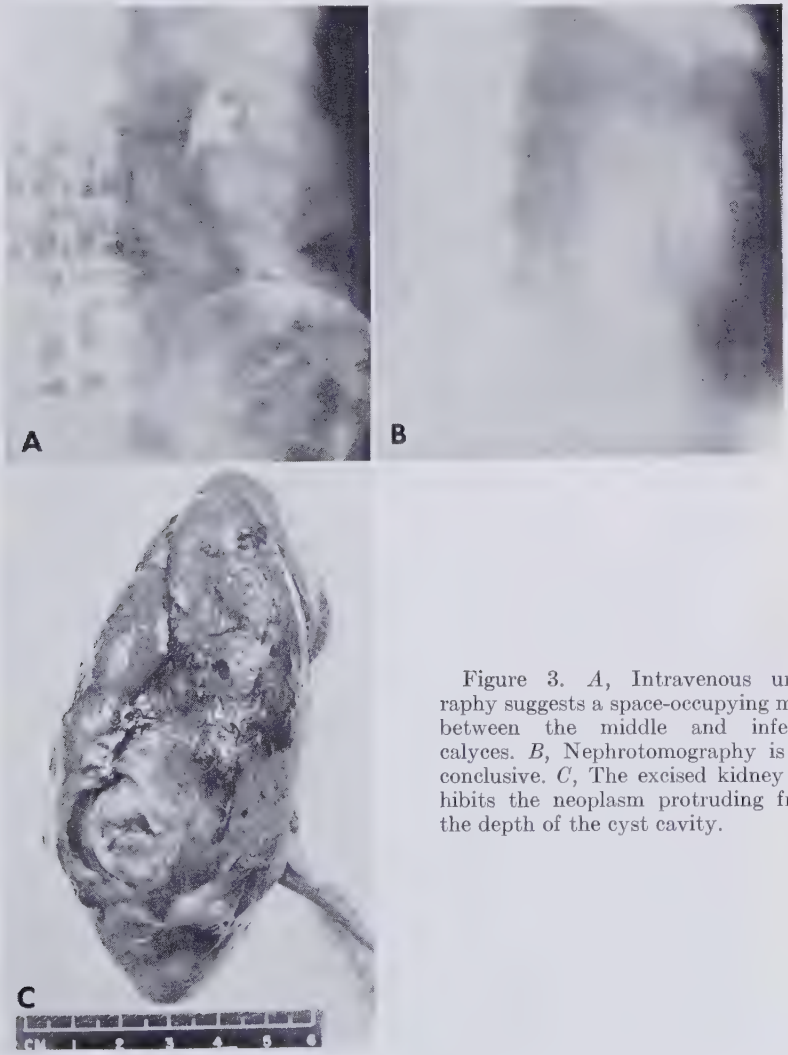


Figure 3. *A*, Intravenous urography suggests a space-occupying mass between the middle and inferior calyces. *B*, Nephrotomography is inconclusive. *C*, The excised kidney exhibits the neoplasm protruding from the depth of the cyst cavity.

space-occupying mass in the lower pole of the left kidney (Fig. 3, *A*). The patient denied any urinary symptoms except incontinence secondary to his neurogenic bladder dysfunction. Retrograde pyelograms corroborated the presence of a renal lesion consistent with a benign cyst. Infusion nephrotomography was performed but unfortunately was not diagnostic (Fig. 3, *B*). A renal scintiscan revealed the presence of a "cold spot" in the same area confirming the presence of a mass. Since the patient was a poor surgical risk, translumbar percutaneous aspiration of the tumor was attempted. No fluid was obtained and surgical exploration was recommended. At operation, a cyst 3 cm. in diameter was identified containing clear amber fluid. When the roof of the cyst was excised, a mottled yellowish mass beneath the floor of the cyst membrane was seen (Fig. 3, *C*). A frozen section of this tissue was reported as renal cell carcinoma. The kidney was removed and the patient had an uneventful convalescence.

*Comment.* The preoperative diagnosis was a renal cyst but the "dry tap" introduced the question of a neoplasm making surgical exploration mandatory. The neoplasm was not within the cyst cavity but was intimately adjacent to the cyst wall.

The relationship of cyst and neoplasm brought into focus by the four categories indicates the confusion that may arise in establishing a correct diagnosis.

## OTHER DIAGNOSTIC AIDS

### Renal Scanning

Radioisotope renal scanning can locate the area of a tumor mass in the kidney but is unable to differentiate between a cyst or neoplasm. The tumor site, which is an area of decreased tubular function, has a decreased cellular uptake and therefore appears as a cold spot.

### Aortography

The intimate details of the vascular supply in the kidney can be visualized by aortography. Variations in the vascular pattern connotes the presence of a mass. Widening, spreading and stretching of the blood vessels in a circumferential outline with rare or absent blood supply to the designated central region is indicative of a benign cyst. Increased blood supply, irregular vascular branching and blunt termination of arterioles called puddling favor the diagnosis of a malignant tumor. Aortography may be performed by the translumbar technique, the femoral percutaneous approach and the brachial artery route. Complications with these techniques are common, although with the newer, less toxic contrast media and improved instrumentation, complications are now less frequent. In the hands of the vascular radiologist who reports on thousands of cases, this procedure is simple and can be executed rapidly. When it is only occasionally performed, however, it is a time-consuming procedure, lending itself to a higher incidence of complications.

### Nephrotomography

Nephrotomography, on the other hand, is a simpler procedure requiring less time and is easily performed. This diagnostic modality studies the variations in renal shadow intensity as visualized by tomography of the kidney after rapid injection of a contrast medium into a antecubital vein. Complications are infrequent and usually of a mild nature comparable to those occurring in the routine intravenous pyelogram. Chynn and Evans reported on a series of 500 cases, claiming a 95 per cent differential diagnostic accuracy between cyst and neoplasm. Green et al. claimed 90 to 95 per cent accuracy in their series.

The technique requires preliminary tomography of the kidneys. The skin in the antecubital region is infiltrated with 1 per cent procaine and a Robb-Steinberg needle is inserted in the vein. The circulation time is determined by injecting a solution of 2.5 ml. of 20 per cent dehydrochloric acid (Decholin) mixed with 15 ml. of normal saline. Then 30 ml. of a 50 per cent contrast medium is rapidly injected. (The time lapse between the intravenous injection of Decholin and the bitter taste on the tongue experienced by the patient is equivalent to the time interval for the intravenous contrast medium to reach the renal arterial system.) At this time the circulation time test may be repeated and then 50 ml. of a lukewarm 90 per cent contrast medium is injected within two seconds. Four to six tomograms are made at the time predetermined by the bitter taste noted in the Decholin circulation time. Another method recommended is to prepare a solution containing equal parts of normal saline and 1 ml. of a 50 per cent contrast medium per pound of the patient's weight. This solution is then rapidly infused into the patient within 10 to 15 minutes. The radiologist has about five minutes to take the various tomographic films. Both methods have recorded excellent nephrotomograms.

The diagnosis of the cyst by this technique is based on the appearance of a smooth circular area of decreased density when compared to the surrounding more opaque renal parenchyma. The area of radiolucency is homogeneous and a sharp demarcation from the adjacent area is readily evident. The malignant tumor on the other hand may be of the same density or more dense than the renal parenchyma. Irregular opacification of the neoplasm may be present and several radiolucent areas may be noted indicating tumor necrosis. The malignant mass offers an irregular dense outline, the margins are ill-defined and fade into the adjacent renal shadow. Nephrotomography can differentiate with a high degree of accuracy between a cyst and neoplasm and can be performed wherever the usual x-ray equipment is available.

## DISCUSSION

The clinical symptoms and laboratory patterns of the renal cyst and neoplasm do not contribute significantly to the differential diagnosis but

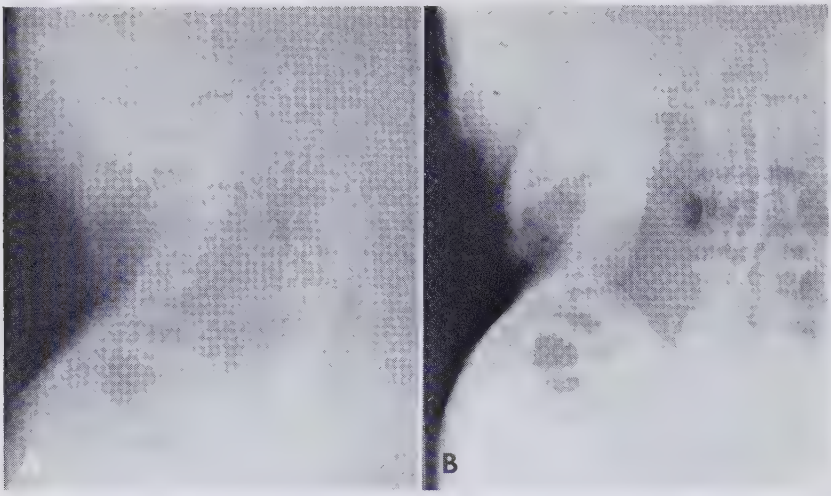


Figure 4. *A*, Note vascular divergence around the space-occupying mass which on exploration was found to be a renal cell carcinoma. *B*, The nephrographic phase again displays an obvious radiolucency simulating a renal cyst.

there is no doubt that they are instrumental in directing the investigation toward a possible renal mass. The differential diagnosis is chiefly accomplished by the various roentgenographic procedures which in the past few years had yielded precise detailed portraits of the kidney structure. Notwithstanding these achievements, the foremost investigators in this field continue to admit a minimal 5 per cent error in diagnosis.

What are the reasons for the misdiagnoses? Basically the physician is human and not infallible. Errors in technique and poor cooperation on the part of the patient may result in qualified radiographic details leading to an inconclusive or questionable interpretation. Repeated studies are not always possible. A malignant tumor can exert occlusive pressure on a small artery or even thrombose the vessel, obstructing the passage of the contrast medium into the tumor mass, and the absence of opaque material in the tumor area will suggest a cyst on aortography and nephrotomography. Compression of the main renal artery by an enlarged neoplastic mass or its regional lymph nodes will reveal a nonfunctioning kidney on pyelography. The same situation can occur when the renal vein is totally obstructed by an invasive tumor thrombus. Extensive central necrosis of a neoplasm can simulate a renal cyst on radiographic studies and the blood supply of the compressed rim of tumor tissue may imitate the vascular details of a cyst (Fig. 4, *A*, *B*). A small tumor located in one area of a renal cyst can be easily missed on aortography. Percutaneous aspiration of clear fluid indicating a benign cyst ignores the possibility that a malignant tumor may be located in another section of the same kidney. These explanations to justify the diagnostic failures only serve to emphasize that the absolute in correct roentgenographic interpretation has not been reached.

At this point the congenital polycystic kidney must be separated from the solitary simple cyst and multicystic kidney. Bricker and Patton have demonstrated that the cysts in the polycystic kidney are dilated sections of functioning nephrons. Puncture or partial removal of these cysts is detrimental to renal function, therefore surgery is ill advised and nephrectomy, except as an emergency measure, is contraindicated. Further discussion on cysts will be limited to the simple and multicystic renal lesions.

When the diagnosis of a renal neoplasm is made there is no controversy regarding surgical excision, nor is there any dispute concerning exploratory surgery when translumbar percutaneous aspiration of a renal mass reveals hemorrhagic fluid, or when a "dry tap" indicates a solid tumor. Underlying the various studies on space-occupying lesions of the kidney is the subconscious impression that surgery should be avoided when a renal cyst is discovered. The concept that a benign cystic mass of the kidney should not be subjected to surgical exploration is mistaken. Aortography and nephrotomography should be utilized to differentiate between the cyst and neoplasm expressly for the purpose of orienting the surgeon in his approach to the kidney. The diagnosis of a malignant tumor is an indication for a radical nephrectomy and surgical approach is altered to favor a primary exposure of the renal vessels with minimal manipulation of the tumor mass. Thus, instead of the routine flank incision the thoracoabdominal, transperitoneal, or an incision through the bed of the eleventh rib would be preferred. Following ligation of the renal vessels, the kidney with the entire perirenal fat and fascia can be removed in toto. In the face of a questionable diagnosis or when a renal cyst is suspected, the kidney is exposed through the conventional flank approach.

Although the renal cyst is a benign tumor, it is not an innocuous lesion. The possibility that it may camouflage a malignant tumor, as reported by Uson, Rehm and Ritter, is real. An inadequate follow-up of these patients may have disastrous consequences. It is this group that falls into the 5 per cent category of radiographic diagnostic failures. The renal cyst pursues an unpredictable course since it may remain stationary in size for years or show a slow progressive enlargement. Continual roentgenographic observation will reveal changes in the kidney structure and the gradual destruction of the renal parenchyma by pressure necrosis. This can be quite extensive, resulting in moderate impairment of kidney function.

Case IV. D.D., a 32 year old white man, was admitted to the medical service in January, 1964 because of hypertension. In 1952 he was treated for glomerulonephritis and in 1953 entered this hospital with a mediastinopericarditis of unknown etiology. At that time an intravenous urogram was reported as normal (Fig. 5, *A*). On admission his blood pressure was 260/160 but on bed rest decreased to 130/90. The hemogram was normal. The urine showed a 3+ albumin and a specific gravity of 1.015. There were 2 or 3 white blood cells per high power field on microscopic examination. The blood urea nitrogen was 20 mg. per 100 ml. The urine culture showed no growth. The intravenous urogram revealed a globular mass about 12 cm. in diameter at the lower pole of the right kidney causing compression and elevation

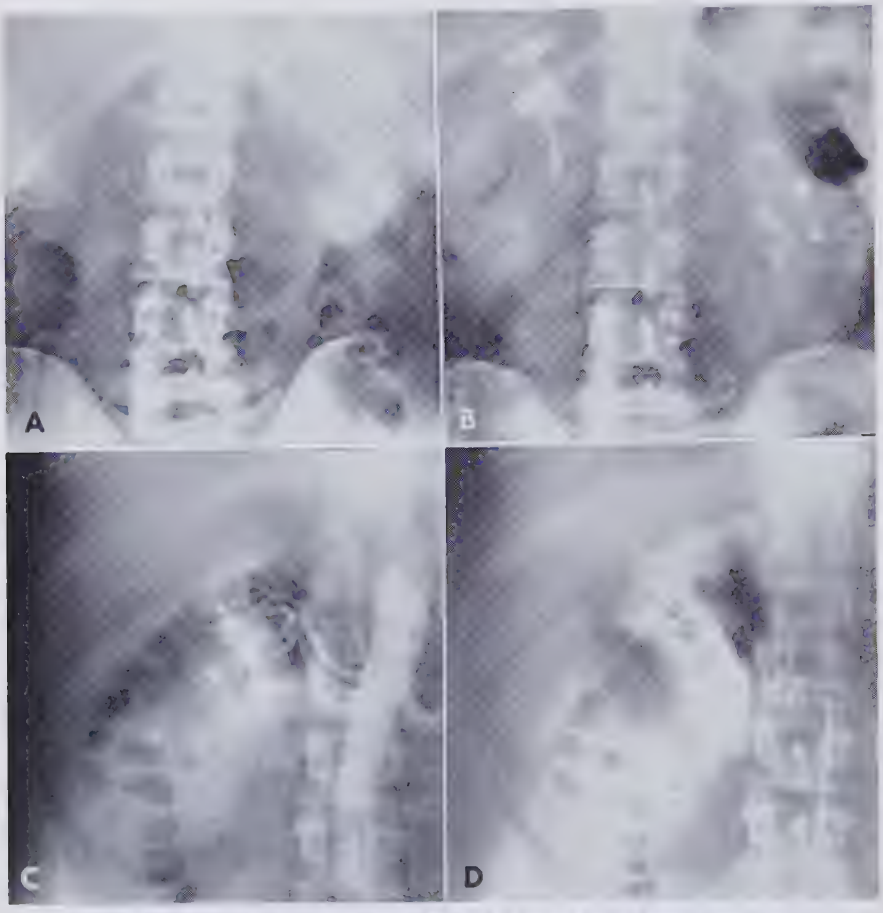


Figure 5. *A*, Intravenous urogram in 1953. Note right kidney is smaller than left. *B*, Intravenous urogram in 1964 reveals a larger right renal shadow secondary to lower pole mass. *C*, Femoral aortogram demonstrates absence of vascular pattern in area of tumor. *D*, Nephrogram illustrates comparative radiolucency of cystic mass.

of the inferior calyces (Fig. 5, *B*). Percutaneous femoral aortography confirmed the diagnosis of a renal cyst (Fig. 5, *C*, *D*), which was explored and unroofed. Postoperative convalescence was uneventful and on a 5-month follow-up examination the blood pressure was 146/90.

*Comment.* This patient presented two interesting features. The first was the extensive destruction of renal parenchyma by a slow-growing benign cyst; the other, the hypertension. When the patient was ambulatory the elevated blood pressure was probably due to the heavy cyst mass causing prolonged stretching and narrowing of the renal artery, resulting in renal ischemia. On bed rest the kidney returned to its normal position, tension on the renal artery was eliminated, renal blood flow improved and the blood pressure returned to normal. Since removal of the cyst mass and

elimination of the renal artery tension, the blood pressure has remained within normal limits.

The renal cyst is usually the source of persistent flank or abdominal pain secondary to distention of the renal capsule, and the weight of this liquid-filled cavity is the cause of an uncomfortable pulling or dragging sensation. The previously mentioned clinical symptoms of gastrointestinal distress, hematuria, anemia and polycythemia may be present, and not to be omitted is the possibility of traumatic rupture of the cyst as well as infection. The renal cyst therefore is not benign but a source of concern and a threat to the continued health of the patient.

In arriving at a diagnosis of a cyst of the kidney which might defer an operation, the risk of the various radiographic modalities must be taken into consideration. These procedures are not without serious complications. Improved contrast media have reduced the incidence of severe toxic complications but mild complications due to technical errors still occur.

In reviewing the entire problem of the cyst and neoplasm, and acknowledging the clinical symptomatic disabilities caused by the cyst, one can only conclude that the diagnosis of a space-occupying mass of the kidney should be an indication for operative intervention. There are, however, certain contraindications to surgery and in this category are the elderly, the cardiac and the otherwise listed poor-risk patient. There is general agreement that conservative therapy and continued observation are the favored methods of treatment of these patients, who should be followed by semi-annual or yearly roentgenographic studies.

CASE V. E.P., an 82 year old white man, was admitted to the surgical service in January, 1960 with a 2-month history of gastrointestinal hemorrhage and melena. The patient had an episode of hematemesis prior to admission and admitted a weight loss of 36 pounds during the past year. A history of gallbladder disease associated with right upper quadrant abdominal pain was obtained. Physical examination revealed a normal blood pressure, an enlarged liver, ascites, and edema of the lower extremities. There was a movable palpable mass in the right upper abdomen. Laboratory studies revealed an elevated blood urea nitrogen of 31 mg. per 100 ml. The hemogram showed a hemoglobin of 9.8 gm., white blood cells 4100 with a normal differential count. The urine was loaded with white blood cells, showed 2+ albumin and the specific gravity was 1.020. The serum alkaline phosphatase ranged from 18 to 52 units and the bilirubin 2.4 to 9.0 gm. per 100 ml. The cephalin flocculation was 4+. Esophagoscopy revealed extensive varices. The gastrointestinal x-ray series demonstrated a sliding hiatal hernia. The intravenous urogram revealed an enlarged right kidney with a deformed calyceal structure (Fig. 6, *A*). The patient was declared a poor surgical risk and since the renal mass suggested a benign cyst a translumbar percutaneous aspiration was performed. Clear amber fluid was removed and a contrast medium was injected. The roentgenogram revealed a smooth, circular outline consistent with a renal cyst. Cytology of the fluid was negative for neoplastic cells. The patient died 13 days following this procedure of a massive gastrointestinal hemorrhage secondary to the esophageal varices and biliary cirrhosis.

*Comment.* This patient was unquestionably a poor surgical risk.

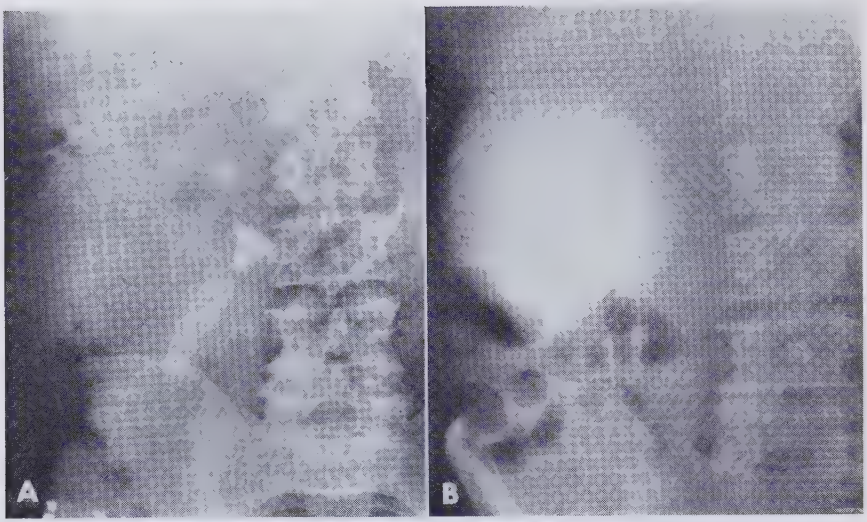


Figure 6. *A*, The intravenous urogram shows the medially displaced pelvis and calyces by a large mass which fills the entire kidney. *B*, Percutaneous introduction of contrast media into the renal mass reveals the smooth round contour of a cyst.

Translumbar percutaneous aspiration was well tolerated and confirmed the pyelographic diagnosis.

When clinical complaints of pain, abdominal distress or other symptoms are associated with the renal cyst, conservative intervention by translumbar percutaneous aspiration can be performed. When hemorrhagic fluid or a "dry tap" indicating a solid tumor is obtained, then surgery is advisable. Surgery of the renal cyst is not a formidable procedure. It is a simple operation performed through a lumbar retroperitoneal approach and is completed in a short period of time. The greatest risk incurred by the patient exists during his lateral positioning while under anesthesia. At this time there is a period of hypotension which can readily be controlled by the anesthetist. The operation consists of exposing the renal cyst and decapping the external cyst wall. Excision of the entire cyst membrane is unnecessary and results in troublesome hemorrhage with prolongation of the procedure. The cyst cavity is drained for two to three days. The operation is well tolerated with a minimal morbidity.

## SUMMARY

The space-occupying mass of the kidney is usually a benign cyst or neoplasm and the presence of a renal mass is an indication for surgical exploration. Radiographic modalities differentiating between cyst and carcinoma are most helpful to the surgeon in determining his operative approach to the renal tumor. Contraindications to surgery in the presence

of a renal cyst are limited to the poor-risk patient. The case may remain under observation but if clinical symptoms warrant, conservative therapy by translumbar percutaneous aspiration of the cyst may be recommended. When the aspirated fluid is hemorrhagic, operative intervention must be considered.

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# Urinary Calculus Disease

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Stones in the urinary tract were known to the ancients and are still with us today, affecting both sexes and showing no respect for one's social or economic status. Urinary stones are a serious problem in sheep, cattle and the household pets, cats and dogs. They also occur in the horse and in wild animals such as mink and porcupine.

The treatment of urinary calculi today is primarily surgical, whether by open operation, endoscopic extraction, litholapaxy or, rarely, dissolution by irrigation, and the indications for surgical treatment and the techniques employed are well known and fairly well standardized. This paper will be concerned, therefore, with those aspects of urinary calculus disease which may not be so well known but which are essential for optimum patient care.

The etiology and pathogenesis of urinary calculi is still a subject of speculation, but clearer concepts are gradually emerging, especially with regard to the factors which affect solubility and crystallization of the calculus-forming salts. Over the past several years a number of ill-founded hypotheses have been discarded. It was formerly thought that urine was continuously supersaturated with calculus-forming salts and that stone formation was prevented by the action of protective colloids. Treatment with hyaluronidase based on the foregoing hypothesis and the administration of vitamin A and salicylates based on other hypotheses have proved to be of no value.

It has long been known that calculi are composed of two principal components, a mucoprotein matrix and a crystalline aggregate. Recently, research and thinking with regard to the essential factors in stone formation has run along two more or less parallel lines. On the one hand, the mucoprotein matrix has been the subject of considerable investigation with the hypothesis that the matrix itself was in some way specific and initiated the process of stone formation.[1] However, today it appears that the mucoprotein matrix is nonspecific and nonessential. On the other hand, increasing awareness of the crystalline nature of calculi has resulted in expanded

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study of the crystalline components. Quite recently Vermeulen[14] has shown that calculi may be grown in the laboratory from urine which has been deproteinized by ultrafiltration and artificially supersaturated. This is a most significant observation and confirms both the nonessential nature of the matrix and the importance of factors affecting solubility and crystallization. Calculi grown in the laboratory are comparable in structure and composition to those found in the human body.

One of the single most important advances in our understanding of why stones may form in the urinary tract was the introduction of the polarized light microscope as a diagnostic tool. In this country Prien and Frondel[11] were the first to point out the advantages of identifying the actual crystals rather than merely noting the presence or absence of certain elements by chemical analysis. Moreover, dissection of a calculus under $\times 10$ to $\times 20$ magnification and identification of the crystal layers under polarized light has shown that calculi are formed in a limited number of specific structural and crystalline patterns. Crystal growth in stones obeys the same fundamental laws governing crystal growth elsewhere in nature.

Today we know that the crystalline components of calculi are for practical purposes limited to the following: calcium oxalate, basic calcium phosphate or apatite, magnesium ammonium phosphate hexahydrate or struvite, uric acid and cystine. Brushite, the more acid form of calcium phosphate, occurs rarely and incidentally occurs nowhere else in the human body. Accordingly, calculi may be classified according to their composition (see Table 1).

**Table 1.** *Classification and Incidence of Renal and Ureteral Calculi in Hospitalized Patients*

*Oxalate*
Pure calcium oxalate, either whewellite ($CaC_2O_4 \cdot H_2O$) or weddellite ($CaC_2O_4 \cdot 2H_2O$), or nucleus and principal portion of stone composed of calcium oxalate with small amounts of apatite as an adventitious surface deposit
Incidence: 54 per cent

*Phosphatic*
Pure apatite or apatite plus struvite—usually about a 6:4 ratio when struvite is present. Apatite is basic calcium phosphate ($Ca_{10}(PO_4)_6(OH)_2$) and struvite is $MgNH_4PO_4 \cdot 6H_2O$.
Incidence: 21 per cent

*Mixed Oxalate and Phosphate*
Interlayered apatite and calcium oxalate usually without a great preponderance of either mineral
Incidence: 10 per cent

*Uric Acid*
Usually pure uric acid
Incidence: 3 per cent

*Cystine*
Usually pure cystine
Incidence: 1 per cent

## STONE TYPES AND THEIR MANAGEMENT

Proper management of the calculus patient requires some knowledge as to the composition of the stone and the essential chemistry of the common calculus components. The characteristics of each type of stone will be considered in reverse order of their occurrence.

### Cystine

Cystine was first discovered in bladder stones by Wollaston in 1810. It was thought to arise from the bladder (hence, the name cystine) and not until 1820 was its renal origin established.[13] Cystinuria is now known to be an inherited disease characterized by an abnormally high urinary excretion of cystine, lysine, arginine and ornithine resulting from a defect in tubular reabsorption. All degrees of cystinuria occur but calculi develop only in those individuals excreting the largest amounts of cystine. Once a stone has formed in a given individual, the tendency is for more stones to form. At the present time it is not known why one person will form a stone at the age of one year and another not until the age of 40.

Cystine stones are the result, first, of the limited solubility of cystine in aqueous solution and, second, its increased concentration in urine. Dent[3] has shown that the urine of cystinurics is apt to be just undersaturated during the day but supersaturated at night because of the lower night volume. He has made this the basis of a medical program which consists of water intake sufficient to provide a urine flow of 2 ml. per minute throughout the 24-hour period. This involves drinking about 600 ml. of liquid every four hours day and night. The concentration of cystine in urine may also be reduced by a low methionine diet (Smith, Kolb and Harper[12]). The diet has been shown to be effective but is so unpalatable that it is doubtful that many patients can successfully adhere to it. D-Penicillamine given by mouth combines with cystine in the urine to produce soluble compounds. This treatment was recently introduced by Crawhall, Scowen and Watts[2] and appears to be the most promising solution to the problem of the calculus-forming cystinuric patient. A morbilliform or exfoliative rash has been reported to occur in some patients following its use. Its chief drawback, however, at the present time is its cost and its status as an experimental drug. Although the solubility of cystine is increased above a pH of 7.6, such a high urinary pH level is difficult to maintain, requiring doses of the order of 30 grams of sodium bicarbonate daily. With the exception of alkalinizing the urine, which is of doubtful value clinically and may promote the formation of phosphatic calculi, all of the above programs have been effective in preventing calculus recurrence and, in some instances, have resulted in dissolution of existing stones.

There is nothing characteristic of the x-ray appearance of cystine stones. They are radiopaque owing to the sulfur content of cystine. Cystinuria should be suspected in any patient with a history of recurrent

calculi or in any child with a stone. Although more sophisticated methods are required for a quantitative determination of urinary cystine, cystinuria may be detected by the following simple test:

To 5 ml. of urine add several drops of concentrated ammonium hydroxide and 2 ml. of freshly prepared 5 per cent sodium cyanide. Mix and wait 10 minutes for the reduction of cystine to cysteine. Add dropwise some freshly prepared 5 per cent sodium nitroprusside. A deep-purple color which fades gradually is a positive result for cystine.

### Uric Acid

Stones composed of uric acid rank next higher in frequency to those of cystine and account for 3 to 10 per cent of all urinary calculi. The relationship between clinical gout, hyperuricemia and the incidence of uric acid calculi is well known. However, not all patients with uric acid calculi have hyperuricosuria. The fact that the solubility of uric acid increases with pH has been known for a number of years, but only recently have the quantitative aspects of this factor been documented in human urine. Fried and Vermeulen[7] have recently shown that the solubility of uric acid in urine may be doubled by increasing the pH by one unit. Since patients with uric acid calculi characteristically excrete a constantly very acid urine, this factor alone is probably the essential one in uric acid stone formation. If the urinary pH is raised from a mean of 5.0 to a mean of 6.0, still within the normal range, the solubility of uric acid in urine will be doubled and the likelihood of stone formation markedly reduced.

Elevation of urinary pH in gouty patients is usually a difficult procedure. The optimum amount of oral base (such as sodium bicarbonate) must be determined for each individual by means of repeated urinary pH measurements. Forcing fluids, as in the treatment of cystinuria, is also useful.

Fortunately, most uric acid stones are small and pass spontaneously. An occasional renal pelvic stone may attain considerable size but staghorn

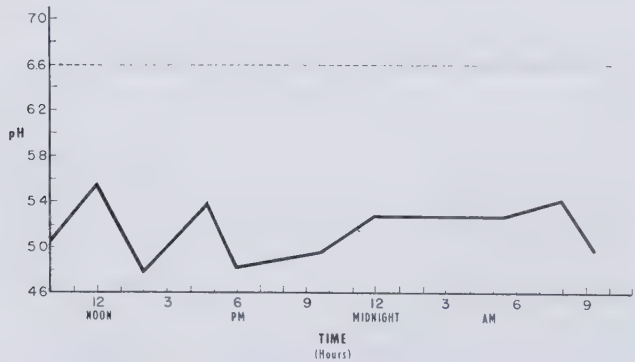


Figure 1. Diurnal urinary pH variation in a patient with gout.

type stones destructive of renal parenchyma are rare. Uric acid stones are nonopaque during x-ray examination of the urinary tract. In the presence of contrast media, they may cast a negative shadow. The gouty patient is prone to intermittent bouts of hematuria and the passage of uric acid crystals ("brickdust") in the urinary sediment. An example of the relatively fixed low urinary pH characteristic of the gouty patient is shown by Figure 1. This may be contrasted to the diurnal fluctuations of normal patients shown in Figure 2.

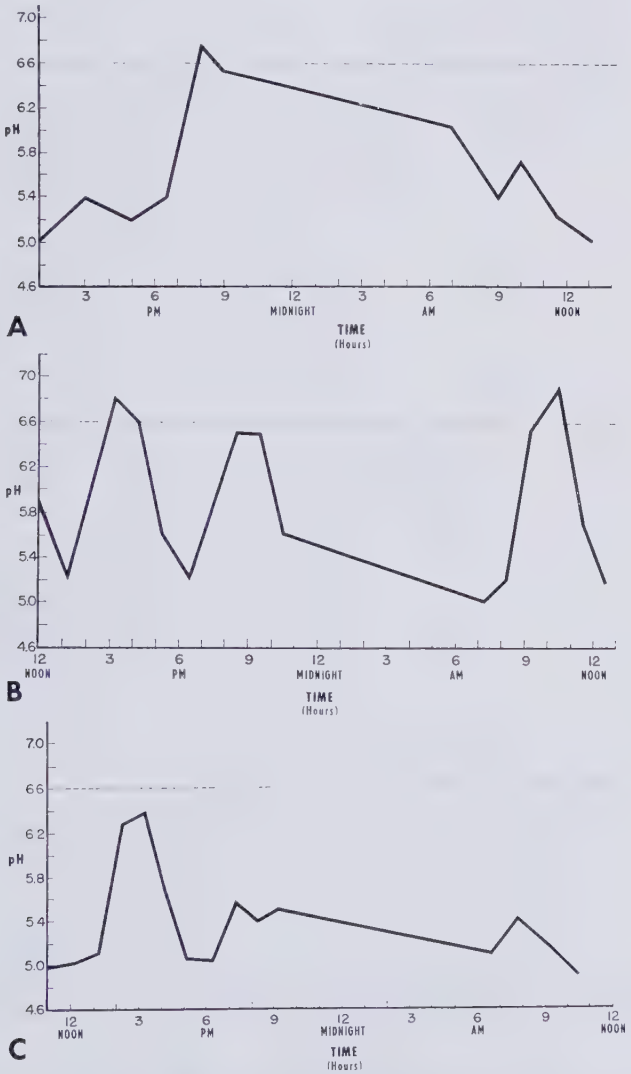


Figure 2. Diurnal urinary pH variations in normal persons. Note the wide swings in *B*.

**Phosphatic Stones**

Although the close association between alkaline urine and the formation of phosphatic stones is a very old clinical observation, the quantitative aspects of calcium phosphate solubility in urine have received attention only within the last few years, much of it in our own laboratory.[4, 5, 6] In simple salt solutions which are saturated with calcium phosphate, the solid phase may either be apatite or brushite, depending upon the calcium to phosphorus ratio and the pH of the solution at equilibrium. For solutions in which the calcium to phosphorus ratio approaches unity, the solid phase is brushite below a pH of about 6.2 and apatite above a pH of 6.2. However, in urine in which the concentration of phosphorus usually is seven to ten times that of calcium, the "conversion" pH is 6.6. We purposely produced a number of urine specimens that were saturated with calcium phosphate by artificially raising the urinary pH. We then compared the solid phase identified by examination under polarized light with the final solution pH. In no instance did we find a precipitate of apatite below a pH of 6.6. Furthermore, in no instance did we find a precipitate of struvite below a pH of 7.1. These observations indicate, then, that in order for apatite to crystallize from urine, the urinary pH must usually be 6.6 or higher, and for struvite 7.1 or higher. Furthermore, in salt solutions and urine saturated with and in equilibrium with calcium phosphate, at a nearly constant phosphorus concentration, the relationship of the log of calcium concentration to pH is an apparent straight line. If we then express calcium concentration in terms of milligrams per liter, we obtain a series of curves of the type shown in Figure 3.

Inspection of the curves will show the profound effect of pH on the solubility of calcium phosphate in both salt solutions and in urine. For example, at pH 5.5, one urine specimen held in solution over 400 mg. of calcium per liter and the other about 650 mg. per liter. Assuming a 24-hour urine volume of 1500 ml., these values would correspond to 24-hour excretions of 600 mg. and 975 mg. of calcium, respectively. On the other hand, the calcium concentrations in the pH range from 6.6 to 7.8 were 12 mg. per liter for the dilute urine and 32 mg. for the concentrated urine, corresponding again to a 24-hour excretion of 18 to 50 mg. of calcium. The so-called conversion pH of 6.6 between brushite and apatite is therefore of significance not only with regard to type of crystal produced but also is in the area where the solubility of calcium phosphate is at a minimum. A number of studies have been performed with regard to other factors which might possibly influence the solubility of calcium phosphate in urine, but in comparison to change in pH, these are all relatively insignificant.

Studies of diurnal pH variations in normal persons have shown that the mean urinary pH is 5.85 with only 10 per cent of 251 individual specimens exceeding 6.6 and only 1 per cent reaching 7.2 or higher. These

observations suggest that urine is usually undersaturated with calcium phosphate but may be supersaturated for brief periods during the day in some persons (possibly accounting for the finding of apatite as an adventitious deposit on a calcium oxalate calculus) and that an apatite or struvite calculus results from a sustained elevation of urinary pH. This has been confirmed by the measurement of diurnal pH variations in patients with phosphatic calculi.

Clinically, one finds a consistently elevated urinary pH in patients with urea-splitting infection, those taking oral base such as magnesium-aluminum hydroxide gel or sodium bicarbonate usually for ulcer-like symptoms, in patients with renal acidosis and in patients taking acetazolamide. It is quite clear at the present time that the prophylaxis of phosphatic calculi depends upon the maintenance of a normally acid urine. Reduction of the urinary calcium by dietary manipulation is of little

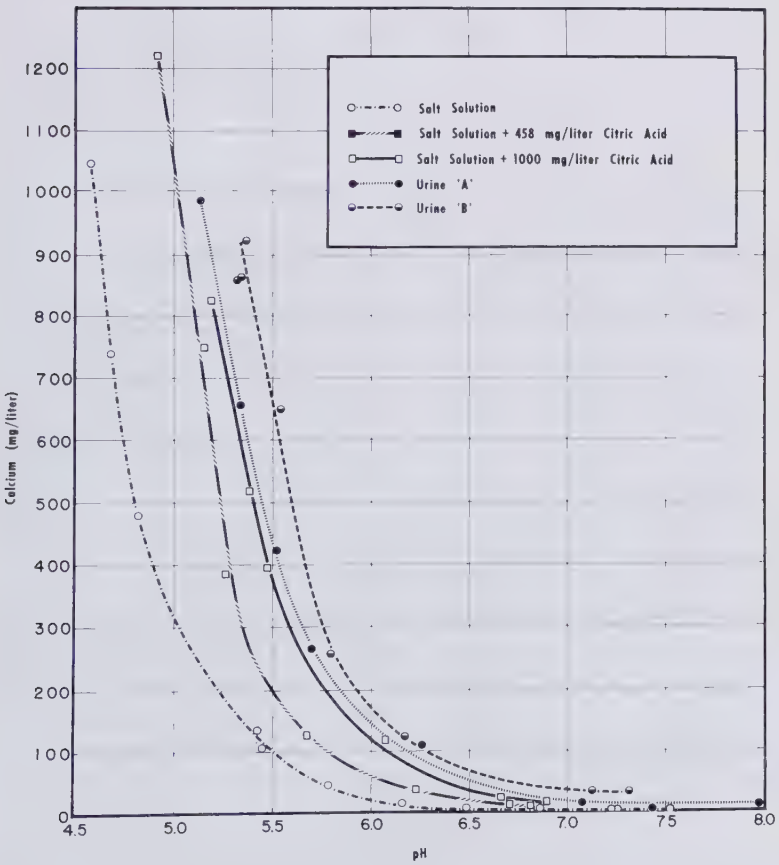


Figure 3. Relationship between calcium in solution and pH in salt solutions and urine saturated with and in equilibrium with solid calcium phosphate. The phosphate concentration is constant throughout.

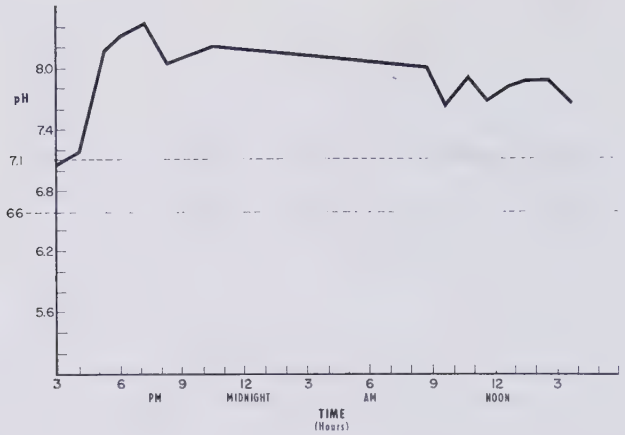


Figure 4. Diurnal pH variation in patient with phosphatic calculi and urea-splitting urinary infection.

significance and, in the presence of a consistently high urinary pH, is of no value.

The presence of a phosphatic stone may be anticipated if the patient has a radiopaque calculus and a consistently elevated urinary pH (see Fig. 4), a urinary infection with Proteus or a history of taking antacid medication. In order to establish the presence of a significant elevation of urinary pH, it is necessary to measure the pH several times during the 24-hour period, since transient rises may occur in normal persons. Although Proteus is the one organism which consistently causes a high urinary pH due to the production of ammonia, other organisms such as Staphylococcus albus and rarely members of the colon group may at times do the same thing. Therefore, urinary bacteria in the presence of a calculus must be tested for their ammonia-producing capability—a simple laboratory procedure. A consistently elevated urinary pH in the presence of sterile urine is due either to medication (oral base or acetazolamide) or to renal tubular acidosis. When an elevated urinary pH is due to medication, the urinary pH will revert to normal after the drug is discontinued.

In the "incomplete" form of renal tubular acidosis, extracellular or systemic acidosis may be absent or negligible (blood chemistry and pH within normal limits) but an acid loading test will show a relatively fixed urinary pH. Seven grams of ammonium chloride are given over a period of one hour in divided doses of 1 gram each in gelatin capsules. Thereafter, urine specimens are collected every hour for at least eight hours and the pH measured. Depending on the severity of the disease, the pH will remain relatively fixed, never dropping below a pH of 5.3 (Wrong and Davies[15]).

The essentials of management in the patient with a phosphatic calculus are: (1) removal of all calculi or foreign bodies; (2) urinary acidification, and (3) long-term suppression of urinary infection. In the presence

of calculi or foreign bodies in the urinary tract, infection will persist in spite of antibiotics. In the presence of infection with a vigorous urea-splitting organism such as Proteus, the urine usually cannot be acidified. Therefore acidification and effective antibiotic therapy should be started after the removal of calculi and catheters. Nonenteric-coated ammonium chloride in doses of 1 gram t.i.d. is a satisfactory drug. After several days of antibiotic treatment and assuming the urine is bacteria-free, the patient should be placed upon long-term suppressive antimicrobial therapy. The drugs of choice are nitrofurantoin (Furadantin) in doses of 50 mg. t.i.d. or a readily excreted sulfonamide such as sulfisoxazole. The urinary pH should be checked several times a day until the urine remains consistently acid for a month. The presence or absence of bacilluria should also be repeatedly determined by direct stain or culture and colony count. Acidification and long-term bacterial suppression should be continued for at least six months and longer if the infection has not been eradicated.

Although very effective in most patients with recurrent phosphatic calculi, this type of treatment has its limitations. The bacteria may not be sensitive to nitrofurantoin or sulfonamides. In some patients with poor renal function or renal tubular acidosis, acidification of the urine may be impossible. Finally, nitrofurantoin given to the uremic patient may produce a severe peripheral neuritis.

### Oxalate

Stones composed principally or entirely of calcium oxalate comprise 50 to 80 per cent of all stones. Of 114 consecutive ureteral calculi examined under polarized light, the nucleus or central core was calcium oxalate in 64 per cent, and it occurred as a secondary or surface deposit in 74 per cent. Just why whewellite (calcium oxalate monohydrate) is found most often in the nucleus and weddellite (calcium oxalate dihydrate) most often as a secondary or surface deposit is not known at present.

Clinically, calcium oxalate stones occur in patients with sterile normally acid urine. Of 35 consecutive patients observed by us with ureteral or renal calculi, only three had associated infection due to (1) enterococcus, (2) Aerobacter and (3) Pseudomonas when first seen. None showed any evidence of obstructive uropathy other than that due to the stone. Twenty patients gave no history of previous calculi. Twelve patients had had prior stones but only three had had mutiple recurrences. Only one of these had proven hyperparathyroidism. None of the rest showed any evidence of metabolic abnormality and the pattern of urinary calcium and oxalic acid excretion conformed to that of normal persons. Patients with mixed (alternating layers) of calcium oxalate and apatite fall into the same general pattern.

The cause of the average calcium oxalate calculus remains an enigma. It is known that the solubility of calcium oxalate is slightly increased over that in pure water by increasing concentrations of inorganic salts ($Na^+$, $K^+$, $NH_4^+$, $SO_4^=$), somewhat increased by increasing concentrations of

lactic and hippuric acids and considerably increased by increasing concentrations of citric acid and magnesium. However, it is not known under what exact combination of circumstances urine is apt to become supersaturated, which it must be in order for crystals to form and grow. Hyperparathyroidism is one disease known to produce urinary stones composed of calcium oxalate or mixed oxalate and apatite, but just why it does so is still obscure. Hyperoxaluria is the other disease known to cause calcium oxalate calculi. It is a rare disorder characterized by a high urinary oxalate excretion and bilateral renal calculi or nephrocalcinosis beginning in early childhood and progressing to death from renal failure. It is thought to result from a genetically controlled metabolic defect leading to overproduction of oxalate. The diagnosis is made by finding a 24-hour urinary oxalic acid excretion in excess of 50 mg. and usually in the neighborhood of 100 mg.

Both Boyce and Howard[9] have found that recurrent oxalate stone formation may be decreased by increasing the dietary phosphorus. Neutral isotonic solutions of sodium or potassium phosphate are given in quantities of 1 to 3 grams of phosphorus per day. The increased phosphate intake apparently leads to the urinary excretion of a substance which increases the solubility or inhibits the crystallization of calcium salts. The oral administration of magnesium oxide[10] in doses of 420 mg. daily has also been reported to reduce the incidence of recurrent calcium oxalate calculi.

In the average patient with a single calcium oxalate stone who presents no metabolic nor urological abnormality, no specific treatment is indicated at the present time. A low oxalate diet is of no value, since urinary oxalate is almost entirely endogenous in origin.

## DIAGNOSTIC PROCEDURES IN CALCULUS PATIENTS

In any patient with a urinary calculus, a few diagnostic procedures are necessary for adequate evaluation and postoperative management.

PETROGRAPHIC ANALYSIS. An essential step is to obtain a stone for petrographic analysis in order to determine its composition. Certainly, the postoperative care and possibly the choice of surgical treatment will depend on a knowledge of the stone's composition and therefore its pathogenesis and potential for recurrence.

In the event a stone is not available for analysis, the following procedures may make it possible to infer its composition.

X-RAY APPEARANCE. Small to medium sized stones which are very dense are apt to be composed of calcium oxalate. Spicules on the surface are diagnostic. Large, dense staghorns or small to medium sized stones which are not very dense or difficult to visualize are apt to be phosphatic. Stones which are homogeneous (no growth layers visible) and moderately opaque should be suspected to be cystine. Nonopaque stones are, of course, uric acid.

URINARY INFECTION. The presence or absence of bacteria may be ascertained by direct stain of the urinary sediment with methylene blue, or by culture and colony count. The direct stain has the advantage of providing an answer in a few minutes. When infection is present, the bacteria should be tested for urea-splitting activity. This is a simple laboratory procedure requiring only a growth medium containing urea and an indicator which changes color as ammonia is produced. A stone may be presumed to be phosphatic in the presence of urea-splitting bacteria. Calcium oxalate stones usually occur in sterile urine.

MEASUREMENT OF URINARY pH. The patient voids directly into a container containing a few cubic centimeters of toluene every hour during the day and as many times at night as feasible. The pH is measured shortly after collection or, if this is delayed, the urine is stored in a refrigerator. A pH meter is ideal but patients can be taught to use test papers at home.

A sustained low pH in the vicinity of 5.0 is characteristic of gout and uric acid stones. A sustained high pH—over 6.6 for most of the day—suggests a phosphatic stone. Patients with cystine or calcium oxalate stones show a normal diurnal pH range.

TEST FOR CYSTINURIA (See under "Cystine")

TESTS FOR HYPERPARATHYROIDISM. Patients with proven calcium-containing stones should at least be screened for hyperparathyroidism. The most valuable procedures are: (1) repeated serum calcium determinations (experience has shown that the serum calcium of patients with parathyroid adenomas may fluctuate into and above the normal range), and (2) tubular phosphate reabsorption test when the patient has been on a normal phosphate intake. According to Gordan,[8] tubular phosphate reabsorption of less than 74 per cent is diagnostic, but a low phosphate intake may raise an otherwise abnormal rate into the normal range. Measurements of serum phosphate, 24-hour urinary calcium and calcium infusion tests are of little diagnostic value. About 20 per cent of patients with hyperparathyroidism will have an elevated serum alkaline phosphatase and x-ray examination will show subperiosteal bone resorption on the radial border of the middle phalanx of the index and middle fingers. X-ray examination of other parts of the skeleton (e.g., the lamina dura) is of little value in the diagnosis.

In a patient with a "high index of suspicion" such as recurrent calculi without other explanation, repeated examinations should be performed over periods of months to years.

## SUMMARY

In current concept the formation of a urinary stone may be regarded as a process of crystallization. Urinary calculi may be classified on the basis of their crystalline composition and consist of four basic types;

cystine, uric acid, phosphatic and calcium oxalate. Prevention of stone growth is based upon changing the composition of urine to increase solubility or possibly inhibit crystallization. Recurrent cystine stones may be prevented by water diuresis, a low methionine diet or administration of D-penicillamine; uric acid stones by raising the urinary pH; phosphatic stones by maintaining a normally acid urine; calcium oxalate stones by increased intake of inorganic phosphate or magnesium. Except for two diseases, hyperparathyroidism and hyperoxaluria, the cause of the common calcium oxalate calculus remains an enigma.

Overall management of the calculus patient depends upon determining the composition of the calculus by petrographic analysis, measurement of diurnal pH variation, the presence or absence of urea-splitting bacteria, screening tests for hyperparathyroidism, and occasionally diagnostic procedures for establishing the presence or absence of cystinuria, renal tubular acidosis or hyperoxaluria.

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# Idiopathic Retroperitoneal Fibrosis

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In 1948 Ormond[15] reported two cases of ureteral obstruction due to envelopment and compression of the ureter by an inflammatory retroperitoneal process of undetermined etiology. Though a similar condition had been described by Kolischer[9] (1922), only since Ormond's article has it been generally recognized as a clinical entity.

The etiology of retroperitoneal fibrosis is unknown and this is reflected in the number of eponyms found in the literature: Ormond's syndrome, idiopathic retroperitoneal fibrosis, Gerota's fasciitis, perirenal fasciitis, nonspecific retroperitoneal inflammation, sclerosing retroperitonitis, sclerosing lipogranuloma, retroperitoneal vasculitis with perivascular fibrosis, etc.

The lesion is a retroperitoneal fibrotic plaque, grayish-white to pink in color. The most common and severe site of involvement occurs in the region where the ureters pass over the iliac vessels, but the extent of the fibrosis can vary considerably. The process has been referred to as a Gerota's fasciitis,[8] however, as more cases are described, involvement beyond the limits of Gerota's fascia has been reported, i.e., the lower end of the common bile duct[18] and the perivesical tissue.[6, 21] The lesion can obtain a thickness of up to 3 cm., causing constriction and loss of function of the involved structures. The ureters are usually compressed in the lateral margins of the plaque, but, in some cases, permanent structural involvement is reported.

Histologically the predominant element is fibrosis with variable degrees of fat and inflammatory cells, creating a pattern from acute or chronic inflammation to hyalinization. The presence of fat-filled macrophages and giant cells has suggested a cytolysis of fat cells with free fat evoking a

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sclerosing lipogranulomatous reaction as an etiologic possibility.[2] The inflammatory cells, noted in many of the early cases reported, suggested a pre-existent or coexistent infection with foci in the lower urinary tract[1, 11, 14] or gastrointestinal tract.[4]

Hemosiderin granules have been found in the para-aortic lymph nodes and it has been suggested that the fibrotic reaction perhaps represents organization of a hematoma or fibrinous effusion following trauma.[3] Ormond, however, feels that "all the evidence is against this."[16]

The presence of periarterial infiltrates in the plaque suggests an arterial or periarterial origin.[7, 17, 18] This inclusion of idiopathic retroperitoneal fibrosis with the collagen diseases is becoming an increasingly popular theory in the literature.[19] In summarizing the etiology of this condition Ormond states: "The etiology is completely dark as it is in other fibrotic conditions—Dupuytren's contracture, Peyronie's disease, Riedel's struma, sclerosing lipogranuloma, sarcoidosis in its late stages and multiple sclerosis (?), and it may be that the solution of one may lead to the solution of the others."[16]

## SIGNS, SYMPTOMS AND PHYSICAL FINDINGS

Because of the insidious onset of retroperitoneal fibrosis, the presenting symptoms of this disease frequently seem unrelated to the urinary tract unless oliguria or anuria is present. Anuria, when present, is a cardinal symptom and has been found to be the presenting complaint in a considerable number of reported cases.[8] The usual history obtained is that the patient has noted progressive anorexia, weight loss and fatigability over a period of several months. He also complains of a vague indefinite backache in the sacral region, which may radiate to the lateral abdominal and inguinal regions and produce a dragging discomfort in the lower quadrants of the abdomen. This abdominal pain is sometimes relieved by assuming the prone position or with flexing of the lumbar spine. Later in the course of the disease the pain often becomes more severe and radiates down the medial aspect of the thighs or to the testicles. This testicular pain has been attributed to the obstruction of the internal spermatic vessels. The back pain may be so severe that orthopedic consultation is obtained and some patients have been subjected to myelography in an attempt to arrive at a diagnosis. Nausea and vomiting have also been reported among the early symptoms of the disease, but they are apt to be more prominent as the patient develops uremia with its accompanying symptoms. The absence of urinary tract symptoms in the preanuric phase is most striking. Occasionally a patient will report some increased urinary frequency and dysuria, but these are not frequent complaints. This absence of symptoms of urinary tract infection is also a common finding. Impotence has been reported in a few cases.

Later in the course of the disease the patient may develop slight edema of the scrotum, inguinal regions and ankles, and other evidence of venous obstruction in the legs, which is probably secondary to compression of the vena cava. Involvement of the abdominal aorta may produce symptoms of peripheral vascular insufficiency, and this has been the presenting complaint in some of the reported cases. A case of common bile duct obstruction with jaundice secondary to involvement by the fibrotic process has also been reported.[14]

Finally, symptoms referable to the urinary tract may appear. The back pain which originally was described as being present in the sacral area now is located higher up in the costovertebral area. The pain may be unilateral or bilateral, depending upon whether only one or both kidneys is involved. Infection may occur secondary to the obstruction, causing symptoms of frequency and dysuria. The increasing obstruction will cause increasing renal damage and, if the obstruction is bilateral, renal insufficiency with all its manifestations of uremia will appear.

The physical condition of patients with retroperitoneal fibrosis may vary from excellent to critical. Most often the physical examination is not remarkable. The only physical finding which is pathognomonic is a palpable mass over the sacral promontory and this was not a frequent finding in the cases which have been reported. The most common finding is tenderness over both renal areas, but this has been reported as being present in only about 50 per cent of the patients. Abdominal tenderness below the umbilicus is about as common. When hydronephrosis occurs secondary to the distal ureteral obstruction, the enlarged kidneys may be palpable. Hypertension also has been reported as being present in 18 or 26 patients with bilateral ureteral involvement secondary to retroperitoneal fibrosis in one of the reported series.[13] However, most authors have not reported this to be common.

Laboratory studies in this disease are frequently nonrevealing. The most common abnormality noted is an elevated erythrocyte sedimentation rate. A moderate anemia is often present. Once the disease has progressed to the point of renal obstruction an abnormal blood urea nitrogen may be present; however, early in the disease this is usually within normal limits also. Again the paucity of urinary findings is striking although a few red blood cells may be noted on microscopic examination of the urine. Urine cultures usually show no growth of bacteria.

The most revealing laboratory studies are the x-ray findings.[10] Plain x-rays of the abdomen may show disappearance of the fat lines which outline the various retroperitoneal structures, notably the psoas and lumbosacral muscles. This absence of fat planes may assist in identifying a mass of inflammatory tissue obscuring these retroperitoneal structures. An intravenous pyelogram may show delayed function, dilatation of the calyces and renal pelves, or complete obstruction on one or both sides. If the obstruction is apparent, the contrast material gradually tapers, demon-

strating a local narrowing of the ureter, usually located between L-3 and the brim of the pelvis. There is frequently a hydronephrosis and hydroureter proximal to the involved segment. The most classical x-ray finding is a narrowing and medial deviation of the midureter. This finding is best demonstrated by bulb pyelograms, according to Mulvaney, who feels that any study which demonstrates hydronephrosis with hydroureter involving the upper one-third of the ureter should suggest the diagnosis of retroperitoneal fibrosis.[12]

Of almost equal importance in the diagnosis of retroperitoneal fibrosis are the cystoscopic findings. Although the pyelograms often show narrowing of the pelvic ureters, ureteral catheters can usually be passed with ease. This is explained by the fact that the obstruction is secondary to external compression of the ureter, rather than to intrinsic obstruction. It has been noted that once the obstruction has been relieved by ureteral catheterization it frequently recurs following removal of the ureteral catheter. Reinsertion of the catheters may be necessary to tide the patient over until a definitive procedure can be performed to relieve the obstructed kidney.

Diagnosis of this condition is suggested by the history, radiographic and cystoscopic findings. However, the ultimate diagnosis depends upon exploration and biopsy of the lesion. The usual operative finding is a firm fibrous mass of retroperitoneal connective tissue extending from the renal hili to the sacral promontory and laterally to involve the ureters. Cases of involvement of the diaphragm and bladder have been reported. Besides compression of the ureters the aorta and vena cava may also be compressed.

The differential diagnosis for retroperitoneal fibrosis includes the following diseases: Hodgkin's, lymphosarcoma, reticulum cell sarcoma, fibrosarcoma, primary ureteral neoplasms, nonopaque ureteral calculi, endometriosis, metastatic ovarian or testicular tumors, tuberculosis, syphilis and actinomycosis.

## TREATMENT

The type of treatment indicated will depend upon the degree of ureteral obstruction that is present. Talbot points out that the two principles of therapy are: (1) relief of the ureteral obstruction, and (2) preservation of renal tissue.[20] In the acute anuric phase, drainage can be re-established by the passage of ureteral catheters or by nephrostomy. The most commonly used procedure to relieve the ureteral obstruction is ureterolysis. Fortunately, most of the patients do very well after this simple procedure. Often ureterolysis is combined with nephrostomy or ureterostomy at the initial exploration. Some authors feel that the involved portion of the ureter should be reimplanted intraperitoneally; however, the results from simple lysis of the ureter and suturing it in a new position seem to be as good. Mulvaney states that the best form of treatment is segmental

resection of the involved segment of the ureter.[12] This is not usually difficult since the upper ureter is often redundant and of sufficient length to bridge the gap. Hutch has pointed out that patients who are treated with nephrostomy drainage early do the best.[8] This is probably explained by the fact that, once the obstruction is removed and the uremia improves, the problems of delayed healing and infection associated with a definitive surgical procedure are much less. The evaluation of the results obtained with any surgical method is difficult to assess, since spontaneous remissions of bilateral hydronephrosis have been reported following no definitive treatment for the fibrosis, except urinary diversion or freeing of only one ureter.

Radiation therapy has also been tried in the treatment of retroperitoneal fibrosis. Although the results have been disappointing in general, Oppenheimer[14] and Harrow[5] have both reported cases in which there was dramatic response to radiation therapy after all other methods of treatment had failed. In both cases there was symptomatic improvement as well as resolution of the hydronephrosis, which was demonstrated by intravenous pyelography. Steroids and antibiotics have also been tried as methods of treatment. However, there is little evidence to show that they have been of any value in treating this disease.

## CASE REPORTS

During the year 1964 two additional cases of idiopathic retroperitoneal fibrosis were diagnosed and treated at the Minneapolis Veterans Administration Hospital. Although the diagnosis was suggested preoperatively in both patients, each had very extensive medical investigations before the diagnosis was arrived at.

CASE I. M.C. (148771) was a 48 year old railroad switchman who was admitted to the orthopedic service of the Minneapolis Veterans Administration Hospital on 4/30/64 with a chief complaint of persistent low back pain. His symptoms had been present since December, 1963 and had been severe enough at times to be incapacitating. In addition, he had also noted a 30-pound weight loss during this time. He had been hospitalized at two other hospitals and undergone extensive urologic (see Fig. 1, *A*), orthopedic and neurological investigations, all of which had been nonrevealing. Physical examination on admission to our hospital was within normal limits. Abnormal laboratory studies included an erythrocyte sedimentation rate which varied between 58 and 96 mm./hr., a blood urea nitrogen of 26 mg./100 ml. and a 4+ C-reactive protein. Again the patient underwent extensive orthopedic, neurological, psychiatric and medical investigations. Finally a repeat urogram in June, 1964 (Fig. 1, *B*) showed a nonfunctioning right kidney.

The patient underwent an abdominal exploration on 6/18/64 and was found to have the typical findings of retroperitoneal fibrosis. A right ureterolysis was done. The pathology report confirmed the diagnosis. Postoperatively the patient did well; however, he did continue to complain of occasional back pain. A repeat urogram several weeks later showed a hydronephrosis of the left side, so an exploratory

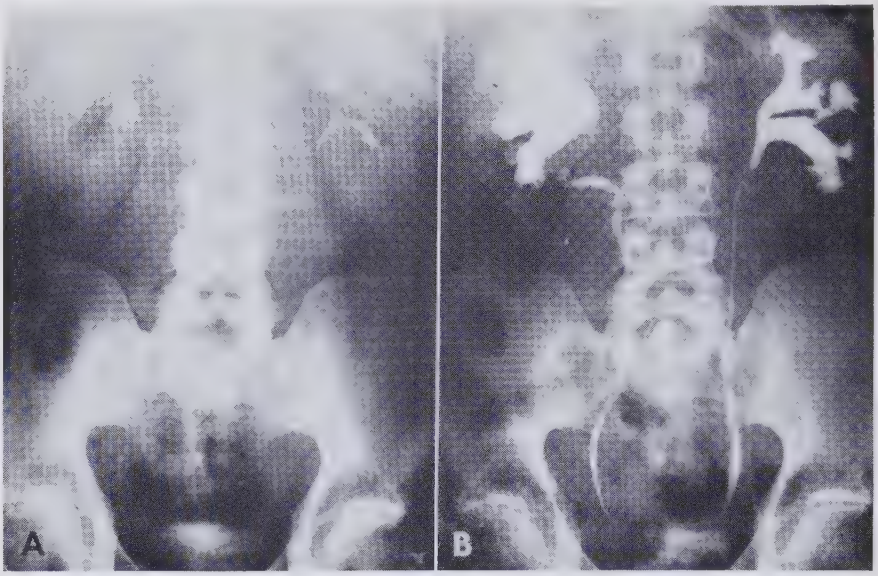


Figure 1. M.C. (148771). *A*, Urogram, March 16, 1964. *B*, Retrograde pyelogram, June 4, 1964.

laparotomy and left ureterolysis were performed on 8/27/64. Following this operation he has been essentially asymptomatic. A follow-up urogram in April, 1965 shows some persistent dilation of the left collecting system, but a normal collecting system on the right side.

CASE II. L.K. (147952) was a 31 year old man who was admitted to the medical service of the Minneapolis Veterans Administration Hospital on 3/9/64 for evaluation of anemia and hypertension. The patient had noted an aching in the right perivertebral area since a hunting trip in November, 1963. This was followed by general malaise. During the interim prior to hospitalization here he had been hospitalized on three occasions and given transfusions for his anemia. Physical examination on admission revealed a pale male with periorbital edema and blood pressure of 130/100. Significant laboratory studies included a hemoglobin of 13.5 grams, which subsequently dropped to 8.9 grams, an erythrocyte sedimentation rate of 70 mm./hr., blood urea nitrogen 96 mg./100 ml. and a creatinine clearance of 2.7 ml./min. The working diagnosis was glomerulonephritis. However, a renal biopsy did not confirm this impression. Urologic consultation was obtained and retrograde pyelograms revealed findings consistent with retroperitoneal fibrosis (Fig. 2, *A*, *B*).

On 4/7/64 the patient's abdomen was explored and he was found to have extensive involvement of the entire left ureter up to the renal pelvis with a fibrotic process. The distal half of the right ureter was involved in a similar process. A left ureterostomy and lysis of the right ureter were performed at this time. His postoperative course was complicated by ischemic necrosis of a portion of the right distal ureter and the development of a ureterocutaneous fistula which necessitated a right nephrostomy and later a ureterostomy. Because of the uremia, healing was poor and the patient developed an extensive wound infection and had a prolonged and complicated hospital course. Since the urinary function of the left kidney was poor, the left ureterostomy was allowed to close. The patient's blood urea nitrogen finally stablized in the range of 50 to 60 mg./100 ml. and he was discharged. He has

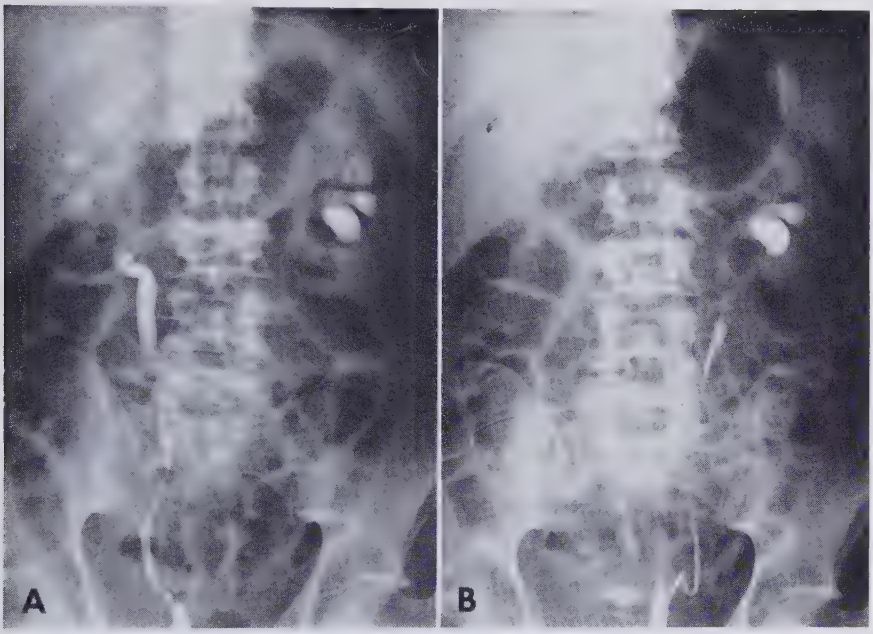


Figure 2. L.K. (147952). *A*, Right retrograde pyelogram, March 30, 1964. *B*, Left retrograde pyelogram, March 30, 1964.

been followed for several months and the blood urea nitrogen has remained fixed in this range. Of interest is the fact that he developed a severe hearing loss, which has been attributed to the prolonged uremia. Presently his cutaneous ureterostomy is functioning well. However, he is unable to return to his former occupation and is unemployed.

In reviewing these cases, two lessons can be learned in retrospect. Although the radiographic studies frequently reveal only unilateral abnormalities, because of the frequency of bilateral involvement both ureters should be examined and transplanted at the time of surgical exploration if indicated. If this had been done our first patient would possibly have avoided a second operation. The second lesson to be learned is that, in the phase of severe uremia, the simplest procedure possible that will relieve the renal obstruction and improve the renal function should be performed. Our second patient's long and complicated hospital course might possibly have been prevented had simple nephrostomies been done at the time of his original surgery.

## SUMMARY

Idiopathic retroperitoneal fibrosis was first established as a clinical entity by Ormond in 1948. The etiology of this condition is still unknown. The pathologic lesion consists of a retroperitoneal fibrotic plaque.

The presenting symptoms of this disease frequently seem unrelated to the urinary tract. Physical examination and laboratory studies are most often nonrevealing. The most classical radiologic finding is a narrowing and medial deviation of the midureter.

Treatment consists of relieving the ureteral obstruction by surgical means.

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# Carcinoma of the Prostate

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One of man's commonest malignancies, carcinoma of the prostate, is occurring more often, probably because of increased longevity, but is being diagnosed more often because of the constantly growing awareness of physicians. Consideration of only clinical carcinoma, or inclusion of postmortem statistics, affects the definition of true carcinoma. In turn, statistics are related to the number of serial sections taken from the prostate at autopsy. Further confusion is produced by the difficulty pathologists often encounter in differentiating less malignant carcinoma from infection or metaplasia in the prostate. Incidence usually is assessed at 10 to 20 per cent of all malignancies in adult males.

Although difficult to diagnose histologically in early states, prostatic carcinoma still presents a typical picture: irregularly shaped cells with large, clear nuclei arranged in glands that are "back-to-back" with only very small amounts of supporting stroma. These cells appear to infiltrate and often are found within perineural lymphatics. Perineural lymphatic invasion alone is not evidence of metastases, although the presence of such invasion generally is necessary to confirm the histologic diagnosis.

Carcinoma has been thought to originate as a small area in the posterior lobe of the prostate. Present evidence suggests that the neoplasm begins as several distinct and separate foci in various portions of the gland, and that this affects significantly the manner of treatment of early prostatic carcinoma.

From its origins in the prostate, the tumor spreads into the seminal vesicles, bladder neck and regional pelvic lymph nodes. There may be extension to any or all contiguous structures, but Denonvilliers' fascia, which separates the prostate from the rectum, usually appears impervious to carcinoma of the prostate. While extension of rectal carcinoma into the prostate is not unusual, infiltration of prostatic carcinoma into the rectum is uncommon.

From the regional pelvic lymph nodes (most commonly, internal iliac), tumor cells may spread to the periaortic nodes and to the cervical, supra-

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clavicular and inguinal lymph chain. Metastases from prostatic cancer are found not infrequently in peripheral lymph nodes.

Besides local infiltration and lymphogenous extension, hematogenous spread is common. This occurs via the vertebral veins, most often affecting the lumbar vertebrae, pelvis, ribs and femurs, in that order of frequency. Hematogenous spread also may involve the lungs and liver.

Invasive prostatic carcinoma of the bone gives a more typical picture. The characteristic glands and cells, still present, produce lysis of bone and perhaps some infiltration of bone marrow. Paradoxically, the metastatic tumor at this state also produces osteoblastic changes on its periphery.

### Etiology

Prostatic carcinoma is found chiefly in men over 55, although not limited to the older male. Because of its relationship to benign prostatic hyperplasia and frequent onset at the time of hormonal alteration, hormonal change has been suggested as the etiologic agent. However, the etiology of prostatic carcinoma has not yet been adequately demonstrated and substantiated.

## DIAGNOSIS

### Symptomatology

Symptoms of prostatic carcinoma appear late and are almost always the result of metastases or local spread. *Early, localized carcinoma of the prostate does not produce symptoms.*

Early diagnosis of prostatic carcinoma depends upon rectal examination, which should be performed at least annually after a man reaches the age of 40. Since symptoms are absent in early stages, only routine, periodic examination allows a chance of finding the tumor early enough to permit curative procedures. The lesion may be identified as a small, hard nodule in the posterior or lateral portion of the prostatic gland. The examiner should note whether the indurated area extends into the seminal vesicles or outside the prostatic capsule. When felt, the area or areas should always be biopsied—*rectal examination alone is not adequate to confirm the diagnosis.*

When the patient first sees a physician, carcinoma usually has spread from its origin in the prostatic lobes and has encroached upon the prostatic urethra and vesical neck, producing symptoms of lower urinary tract obstruction. The tumor usually has extended locally or into the seminal vesicles, or has already caused distant metastases.

If present, urologic symptoms have developed gradually as the prostate enlarged and pressed inward on the prostatic urethra or bladder neck, causing symptoms of prostatism with hesitancy, frequency, diminution in size and force of the urinary stream, and nocturia. Later, symptoms of uremia will be accompanied by weakness, nausea and oliguria. There may be acute

retention as local extension upward into the region of the ureters and near the seminal vesicles obstructs the ureters. Hematuria may occur, but is often a late finding.

Hydronephrosis may produce flank or lower back pain in about 20 per cent of patients by extension of the tumor from the vesical neck or seminal vesicles, and encroachment upon the ureters. Consequent obstruction indicates poor prognosis and often causes death.

Unilateral or, less often, bilateral edema of the lower extremities may occur if the pelvic lymphatics are sufficiently invaded by tumor. When metastases to bone have occurred, the resultant pain is deep, constant and severe. Later, when bone marrow has become involved, marked anemia ensues with accompanying weakness, weight loss, and emaciation.

Cervical, inguinal, or supraclavicular lymphadenopathy may be the presenting complaint, and sometimes is found without evidence of osseous metastases. This usually denotes a very serious prognosis.

### Physical Findings

Physical findings in prostatic carcinoma are principally those demonstrable on rectal examination. In early carcinoma, a small, discrete, indurated nodule may be palpated in the prostate. Such a lesion may be due to prostatic calculi, fibrosis, chronic granulomatous prostatitis or, occasionally, benign adenomatous hyperplasia, as well as carcinoma. Prostatic calculi may be seen radiographically in films of the pelvis, but may occur concomitantly with carcinoma. While prostatic carcinoma ordinarily is described as a stony-hard lesion, 10 to 15 per cent of untreated prostatic cancers that we see are *softer* than normal in consistency. Our suspicions are aroused whenever the prostatic outlines are hazy and indistinct in any area. All such instances are investigated by needle biopsy, and about half show malignancy upon histologic study.

The number of prostatic carcinomas found varies with the examiner's level of suspicion, but about half of the questionable prostatic lesions eventually turn out to be malignant. For this reason, biopsy *proving* carcinoma should always be obtained before instituting therapy.

### Biopsy

Tumor extension beyond the confines of the prostate usually can be palpated as an indurated area. Suspicious areas must be biopsied, and open biopsy is by far the most accurate of several methods. Tissue can be obtained by either the perineal or the retropubic route, but we prefer the *open perineal biopsy*. Since the lesion is most often found in the posterior lobe, perineal approach offers the advantage of direct vision plus the opportunity to excise the lesion accurately. Immediate frozen sections permit radical prostatectomy to be performed immediately if carcinoma is found. When the histologic report is doubtful, the wound can be closed and, later, if the final report is positive, the wound can be reopened without

technical difficulty to allow prostatectomy. Alternatively, radical retropubic prostatectomy through a suprapubic incision achieves advantages of combined abdominoperineal radical prostatectomy.

*Retropubic prostatic biopsy,* in our hands a more difficult procedure, is performed by elevating the prostate from the rectum and rotating the gland to expose the lesion. The principal advantage of this method is the opportunity to inspect the iliac lymph nodes for possible metastatic involvement.

Sometimes, in advanced cases, it may be valuable to use the resectoscope for *transurethral biopsy* of the prostate. However, this technique is not reliable in early prostatic tumor, since the lesion usually arises in the portion of the prostate most remote from the resectoscope.

*Transrectal prostatic biopsy,* or biopsy through the rectal wall, is employed by many urologists, but we do not use it because we feel it is contrary to surgical principles. In preparation for transrectal biopsy, the bowel customarily is prepared with neomycin. After a rectal speculum has been introduced, a needle is passed into the rectal wall in order to remove prostatic tissue with biopsy forceps. This procedure would seem to make subsequent radical prostatectomy more difficult, and to increase the risk of rectourethral fistula.

Second only to open perineal biopsy, the *perineal needle biopsy* has given us the greatest satisfaction. We prefer the Franklin modification of the Vim-Silverman needle. Local anesthesia supplemented with 25 mg. of alpha-prodine (Nisentil) is satisfactory, although thiopental sodium (Pentothal sodium) and nitrous oxide yield excellent results.

Generally, patients are hospitalized for perineal needle biopsy, but it may be performed on outpatients equally well. After induction of anesthesia, a finger is inserted into the rectum. The needle with obturator is passed into the perineum just anterior to the rectum, where it can be felt through the rectum and its point directed to the suspected lesion in the prostate (Fig. 1). It should not perforate the rectum. When the needle's point is against the nodule, the obturator is removed and the cutting blades are inserted and advanced into the lesion. At this point the sheath, or needle, is advanced over the blades. When the blades are encased within the sheath, they are withdrawn and the cylinder of tissue is removed. Now the sheath can be repositioned to obtain another cylinder. Ordinarily, at each biopsy session we take at least five cylinders of tissue, which are placed in formalin immediately and sent for histologic study.

Although easy for the physician to perform and easy for the patient to undergo, perineal needle biopsy is less accurate than open perineal biopsy. If the pathologist reports "no carcinoma," we always perform a second biopsy. If the second report also is negative, we accept it with reservations. In the last seven years, we have seen only one untreated patient who had had two negative needle biopsies but subsequently was shown to have carcinoma of the prostate.

Securing a good biopsy specimen, and its examination by a pathologist able to interpret the nuances of the prostatic pathology, are equally important in confirming diagnosis of malignancy.

Formerly there was much interest in diagnosing prostatic carcinoma by *exfoliative cytology* —the observation of prostatic secretions obtained by prostatic massage. Today this method is seldom used because it is felt that massage vigorous enough to express acinar epithelial cells is liable also to encourage metastatic extension of tumor.

### Radiologic Diagnosis

Radiologic study of the bones is always important in evaluating patients suspected of having prostatic cancer, even though it shows only metastatic lesions and is of greatest value in advanced cases. Even roentgenograms negative for metastases aid in proper staging of the disease. A film of the kidneys, ureters and bladder, with a separate film of the pelvis, usually is adequate for screening, since this includes the bones in which early metastasis most commonly appears. Metastatic lesions usually appear as areas of increased density and may be single or multiple. Although carcinoma of the thyroid can produce similar lesions, fortunately their occurrence in this location is rare. The principal condition causing difficulty

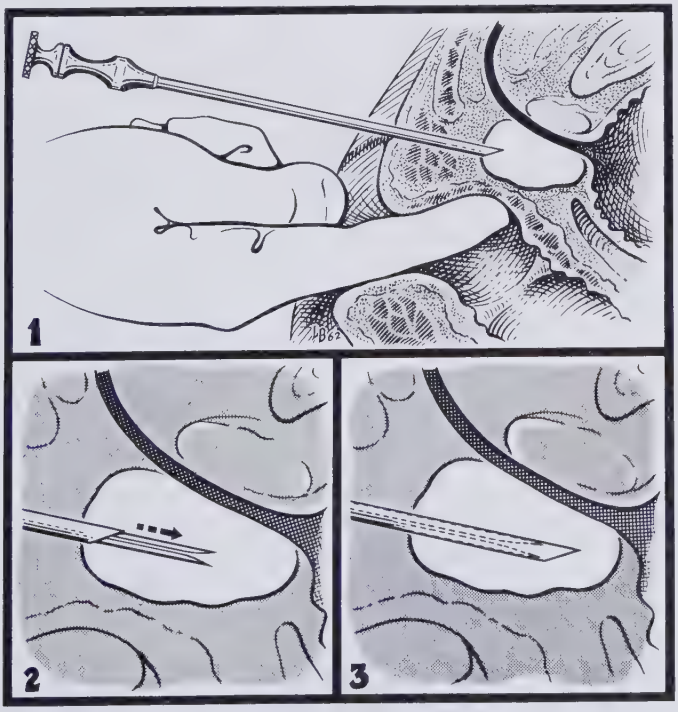


Figure 1. Technique of needle biopsy of prostate. 1. Needle in position for biopsy. 2. Cutting blades inserted into prostatic lesion. 3. Sheath advanced over blades.

in interpretation of these roentgenograms is Paget's disease of the bones, in which the typical trabecular pattern is still present or increased.

Occasionally osteolytic areas occur in prostatic cancer, and sometimes they are seen concomitantly with osteoblastic areas. Osteoblastic areas do not necessarily become less dense as the patient improves under therapy and the metastases diminish, but actually may appear more obvious and denser for a period up to six months. As the period of improvement lengthens, the metastases seem to become less dense. Experience suggests caution in stating that metastases are absent on the basis of roentgenographic examination alone, since metastases are not apparent until quite late, and small or very early metastatic lesions in bone can be missed.

Recently, at the Minneapolis Veterans Administration Hospital, we have performed bone scans using strontium-85; 75 microcuries of radioactive strontium are injected intravenously, and two to five days later areas suspected of osseous metastases are scanned. So far, results have been equivocal in the number of patients studied.

**Acid Phosphatase**

Gutman and Gutman published their classic work on serum acid phosphatase in 1938. Serum acid phosphatase elaborated by cells of the prostatic epithelium is present in high concentrations in prostatic secretions, but ordinarily is not present in the blood stream in large quantities; most of the measured serum acid phosphatase is derived from the blood cells, liver and spleen. However, when prostatic cancer has metastasized to bone, liver or lymph nodes, the acid phosphatase formed by the neoplasm passes into the circulation and produces elevation of the serum acid phosphatase. Such elevation also may occur following any type of prostatic massage, manipulation or instrumentation of the posterior urethra. Rises in serum acid phosphatase are transient, although lasting up to eight hours. To preclude false elevations, blood should be drawn more than 24 hours after rectal examination or any instrumentations.

Other states thought to increase amounts of this enzyme in the blood are hepatic or renal disease, Gaucher's disease, and conditions causing intravascular lysis of erythrocytes. Elevations from such causes are rare and, practically speaking, can be considered almost nonexistent. If blood is collected properly, elevations of serum acid phosphatase can be assumed to indicate distant metastases from prostatic carcinoma.

The Bodansky and King-Armstrong tests are the two principal techniques for measuring serum acid phosphatase. The Bodansky method measures phosphatase released by the hydrolysis of glycerol phosphate; 1 Bodansky unit is regarded as the upper limit of normal in most laboratories. The King-Armstrong technique measures the hydrolytic activity of the phosphatase on a substrate releasing phenol. In our laboratory, 4 King-Armstrong units are considered the upper limit of normal.

In 1949 a technique devised for measuring the "prostatic" portion of

serum acid phosphatase used the inhibition of the "prostatic" portion by levotartaric acid. This makes the test much more sensitive and, in our experience, when the serum has been properly collected, elevation of "prostatic" acid phosphatase always means distant metastases from prostatic carcinoma. We have not yet found a patient with purely local spread, and without distant metastases, whose level was elevated—again stipulating that the serum was collected properly.

Performance of this test is so complicated that it is not feasible for a small laboratory, but the method of collection is simple. The patient must be fasting. Blood drawn from the antecubital vein is allowed to clot. *Immediately* when clot retraction occurs, the serum is withdrawn and centrifuged to remove all erythrocytes, as these contain acid phosphatase and their lysis will influence the test considerably. The supernatant serum is frozen and sent to the nearest laboratory performing the test. For the last three years, instead of freezing the serum we have mixed it with measured numbers of disodium citrate tablets; no significant deterioration has occurred within three weeks. Therefore, this modification permits mailing to even a distant laboratory for accurate determination of "prostatic" and serum acid phosphatase.

We wish to emphasize that distant metastases from prostatic carcinoma do not always produce elevation of "prostatic" and serum acid phosphatase; in about 20 per cent of patients with metastases, acid phosphatase levels may remain normal. *When acid phosphatase levels are elevated, metastases are always present; when levels are normal, metastases may be present or may not.*

Besides roentgenographic changes and alterations of the level of serum acid phosphatase, prostatic carcinoma produces the usual effects on other organs of the body, depending on direction of growth or sites of metastases. Metastasis often is accompanied by marked anemia. Occasionally circulating fibrinolysin in the serum augments the hazards of surgery, although we have encountered it only occasionally. Pyuria or hematuria may be present if the prostatic urethra is invaded by cancer or if it is obstructed. If the ureters are obstructed, azotemia may occur.

## STAGING

Proper staging of prostatic carcinoma is valuable in selecting and beginning treatment. On a practical basis, we prefer the system approved by the World Health Organization on Staging and Progress, used by the Veterans Administration Cooperative Urological Research Group. This divides all prostatic cancers into four stages on results of rectal examination, roentgenographic studies of the skeleton, prostatic or total serum acid phosphatase, and biopsy from the prostate (Table 1). Stage I is "carcinoma-in-situ," or latent carcinoma, or focal carcinoma. Stage II is early carcinoma which can be detected by rectal examination but which has not spread

**Table 1.** *Diagram of System of Staging of Prostatic Cancer*

| PROSTATIC CANCER | | | |
|---|---|---|---|
| Stage | Rectal Examination | Prostatic Acid Phosphatase | X-ray Evidence of Metastases |
| I | No Induration  | < 1.0 K.A.U. | 0 |
| II | Localized Nodule | < 1.0 K.A.U. | 0 |
| III | Extraprostatic Extension | < 1.0 K.A.U. | 0 |
| IV | Equivocal Findings | > 1.0 K.A.U. | + |

K.A.U. = King-Armstrong units.

beyond the confines of the prostate. In Stage III, the carcinoma has spread into the seminal vesicles or outside the capsule of the prostate, without evidence of distant metastases. (Arduino and Glucksman have shown that in a significant number of patients the local or pelvic lymph nodes are also involved.) In Stage IV, distant spread of tumor has involved the liver, distant lymph nodes, bone, or other remote tissues. For purposes of treatment, we consider Stages I and II as surgically curable, and Stages III and IV as incurable, with treatment only palliative.

## STAGE I—DIAGNOSIS AND TREATMENT

Stage I carcinoma (latent carcinoma, focal carcinoma, or carcinoma-in-situ) shows no physical signs suggesting neoplasm on rectal examination, no metastases demonstrable roentgenographically, and no significant acid phosphatase level. It is impossible to diagnose carcinoma at this state except through histologic study of tissue removed at subtotal prostatectomy or prostatic resection performed for any cause. Often nests of carcinoma will be seen in only one or two sections, and the inclination is to consider the carcinoma completely excised. Recent evidence indicates such assumption will be false, and that carcinoma is usually multicentric in origin. Residual carcinoma, existing in most cases, is just as malignant and dangerous as that of any other stage.

Many feel that Stage I carcinomas are less malignant than those of

other stages, and conservative treatment with oral estrogens may be used. This plan may have merit in patients with extremely poor cardiac reserve or those above the age of 80, but such treatment is merely palliative and allows the cancer to remain in the prostate, from which site local spread or metastasis can occur. Since carcinoma at this stage is curable, we consider the only desirable treatment is one which should produce cure—radical prostatectomy.

Radical prostatectomy is merely total prostatectomy with seminal vesiculectomy, the bladder neck being anastomosed to the membranous urethra. The operation, simple for one properly trained in its performance, may be carried out through either a suprapubic (retropubic) or perineal approach. Each has its virtues, but it is best for the surgeon to employ that which has been most successful in his hands.

*Radical retropubic prostatectomy* is performed with the patient supine. A midline or transverse incision is made in the abdomen just above the pubis, and the rectus muscles are retracted, exposing the prostate. The puboprostatic ligaments contain a very large vein, and are ligated before being cut. The urethra is transected and the prostate is raised off the rectum. The seminal vesicles and vasa deferentia are then freed from the surrounding tissue. The prostate is cut from the bladder neck and removed. The bladder neck is sutured to the urethral stump, drains are placed, and the wound is closed. Blood loss should be minimal.

*Radical perineal prostatectomy* is performed with the patient in exaggerated lithotomy position. An inverted-U incision in the perineum exposes the rectal wall and perineal muscles. The levator ani muscles are spread from the midline and the prostate gland is exposed. The rectum is reflected from the prostate posteriorly and the seminal vesicles and vasa deferentia are freed. The urethra is transected, the puboprostatic ligaments are cut, and the prostate is cut from the bladder neck and removed. The bladder neck is sutured to the stump of the urethra and the wound is closed.

The principal complications of these two procedures are impotence, incontinence and rectal injuries. Impotence always results from total prostatectomy, and while it is complete and untreatable, it is a low price to pay for cure of cancer; many patients requiring this operation are already impotent or almost so.

Incontinence, a more serious problem, follows radical prostatectomy less frequently than generally believed. At this hospital among the last 17 men undergoing radical prostatectomy, only two became incontinent according to our definition; one is very senile and the other is out-and-out incontinent. Almost all patients have some incontinence during the first three postoperative months, but sphincter exercises restore complete continence to most within the first six postoperative months. Any type of incontinence clamp or bag is banned on our service, since sphincter action returns only if the sphincter is used, and employment of incontinence bags reduces need for voluntary effort. These measures can and do work.

Although rectal injuries can occur during prostatectomy, their fre-

quency is directly related to the surgeon's skill. Such injuries, usually perforations, happen most commonly when the prostate and rectum are being separated. To prevent rectourethral fistulas, we guard against the off-chance that injury might occur by preparing the patient's bowel.

## STAGE II—DIAGNOSIS AND TREATMENT

When a hard, localized node is felt in the prostate, with neither biochemical nor roentgenographic evidence of metastases, we consider it as Stage II carcinoma. On the basis of present knowledge, *treatment in Stage II carcinoma is radical prostatectomy.* Estrogens, orchidectomy and various types of irradiation or chemicals are contraindicated (in this stage) and radical prostatectomy alone should be performed.

Biopsy is most easily and best obtained by the open method, in which the patient is prepared for radical prostatectomy. The prostate is exposed perineally and the prostatic nodule is biopsied. If frozen sections are positive for carcinoma, radical prostatectomy is carried out immediately; if negative, the perineum is closed. If carcinoma is found in paraffin sections, the wound is reopened and radical prostatectomy is performed. Sometimes, instead of reopening the perineum, we prefer to perform radical retropubic prostatectomy, which is easily done since the prostate is already freed from the rectum.

We mention only to condemn the practice of palpating a prostatic nodule and then "watching it." Presumably this period of observation allows the cancer to become more definite; actually, waiting allows it to progress to an inoperable stage.

It cannot be stressed too strongly: *if in doubt, biopsy!*

## STAGE III—TREATMENT

When carcinoma has progressed to Stage III, spreading through the prostatic capsule, it is no longer curable. Therefore, treatment is necessarily palliative.

Formerly, *hormonal control* of prostatic carcinoma consisted of bilateral orchidectomy, administration of estrogens, or both. The mode of hormonal and antihormonal therapy still is not completely understood. The benefit produced by orchidectomy apparently results from at least partial removal of androgenic hormone upon which the growth of the prostatic malignancy depends. The effect of estrogenic substances is considered due to inhibition of follicle-stimulating hormone (FSH), upon which the androgenic activity of the testes is believed dependent. This inhibition of FSH results also in inhibition of androgen production from extragonadal sources. Also, direct action of estrogens upon prostatic cancer cells themselves has been suggested.

The relative worth of these therapeutic efforts has not been proved. Until more accurate information is available, each must be considered equally effective or ineffective. In the Veterans Administration, a large group study is currently attempting such a comparison.

Stilbestrol is the drug of choice. Other natural and synthetic substances do not seem to bear significant advantage over stilbestrol, which is also one of the least expensive estrogenic substances. The recommended dosage has varied from 0.1 mg. to 500 mg. three times daily. It has been administered intramuscularly and orally. In our experience, 5 mg. of stilbestrol orally each day is best, and there is seldom reason to vary this. When the patient cannot be depended upon to take his stilbestrol, once monthly we inject 40 mg. of Estradurin, a synthetic estrogen, into the gluteal muscles.

Orchidectomy for prostatic cancer should be bilateral and complete. As androgenic cells exist in the testicular capsule, full benefits of orchidectomy cannot be achieved if the testicular capsule remains, as in subcapsular orchidectomy.

Probably the best method of *radiotherapy* is the injection of radioactive gold ($Au^{198}$) into the prostatic tumor itself, as advocated by Flocks. Radioactive gold in a colloidal suspension is injected into the prostate through a retropubic or perineal incision. Since 95 per cent of the radiation emitted consists of short penetrating beta rays and since the half-life of radioactive gold is only 65 hours, undesirable radiation of surrounding structures can be avoided. This material is difficult to handle, and despite Flocks' excellent results, we prefer to reserve its use for the unusual case.

Radioactive Yttrium, radon and radium have been employed. High-energy irradiation has been tried with radioactive cobalt or supervoltage x-ray machines. These are not advocated for general use at present.

Since individual patients with prostatic carcinoma vary widely in their response to different treatments, conclusive results are difficult to state. However, it is our impression that most men treated by orchidectomy will live five years or more with the disease but without major disability.

## STAGE IV—TREATMENT

In Stage IV, distant metastasis has occurred. Serum acid phosphatase may be elevated, and/or there is roentgenographic evidence of osseous metastases, or there is involvement of peripheral lymph nodes. Most of these men live only 18 to 24 months. Occasionally patients in Stage IV live 5, 10 or 15 years after the tumor is discovered, but just as many die within six months after treatment has begun.

Therapy in Stage IV consists of *estrogen* or *orchidectomy*, or both, as in Stage III. Again, no reliable facts recommend one treatment over another. Estrogens seem to offer the greatest value in Stage IV and we prefer 5 mg. of stilbestrol orally each day. Orchidectomy adds little or

nothing to their effect here. When discussing outcome with the patient, the prognosis should always be guarded.

Treatment may show dramatic results, with the serum acid phosphatase level dropping rapidly, often to normal. Appetite improves, the blood hemoglobin increases, the patient gains weight and strength and looks well again and, from most parameters, feels better, yet roentgenograms of the bones show little or no change from films made before treatment. Symptoms usually recur within 18 months, signaling a downward course. Reasons for regression are presently unknown, but androgen secretion by the adrenal in response to hypophyseal stimulation, or escape of the adrenal from the antiandrogenic effects of estrogen, are possibilities.

Certain procedures may be worthwhile, such as *bilateral adrenalectomy* to extirpate completely possible sources of androgen. Relief of pain appears to be the principal result, with little or no remission in progress of the disease. So-called "medical adrenalectomy," using cortisone, inhibits pituitary production of ACTH, thereby suppressing the output of adrenal androgens.

*Cortisone* administered for prostatic cancer in remission should be given in an initial dosage of 200 to 300 mg. daily, later holding at a maintenance dose of 100 mg. daily. Since cortisone produces considerable sodium retention, prednisone is probably better, employing an initial dose of 40 to 60 mg. and a maintenance dose of 20 to 40 mg. daily. Antacids should be used with these drugs to reduce the likelihood of peptic ulcer.

*Hypophysectomy* may be a last resort in prostatic carcinoma that is becoming resistant to hormonal therapy. We have used it in only a few cases, without noteworthy results.

Of many other drugs used in progressing prostatic carcinoma, probably the best is *diethylstilbestrol diphosphate* (Stilphostrol), 1 gram in 500 cc. of 5 per cent dextrose in distilled water, administered as an intravenous drip. This should be given quite slowly, since fast administration generally causes sensations of perineal heat, probably from concentration of the drug in the prostate. It is used daily for five to ten days initially, and then should be given every month, 1 gram daily for five days.

Chemotherapy has been of debatable value.

Carcinoma of the prostate is relatively radioresistant, but adequate dosage sometimes produces regression of the lesion. In treating metastases, deep *x-ray therapy* is directed to individual osseous lesions, or intravenous injections of radioactive phosphate are given. For individual bone lesions, a dose of 2000 to 3000 r is considered adequate and marked relief of pain in the irradiated area can be expected. Such therapy is particularly useful in prostatic cancer metastatic to the hip when weightbearing has been interrupted because of severe pain, but should be used cautiously, since pain may be a protective mechanism shielding weak bones with thin, easily fractured cortices.

*Radioactive phosphate* ($P^{32}$) may be given orally or intravenously,

although intravenous injection usually is preferable. It seems to concentrate principally in prostatic lesions of bone, where its soft beta rays irradiate the metastatic areas without seriously affecting hematopoietic tissue. When radioactive phosphate is used, estrogens are discontinued and testosterone is begun, in order to increase the percentage of $P^{32}$ uptake. Shortly after administration of the isotope, pain should be relieved and improvement should be apparent.

Along with such measures, which can be considered specific for treatment of prostatic cancer, other nonspecific measures should be utilized. Anemia usually is much more severe than would be expected from radiologic appearance of the bone or from the bone marrow biopsy hemogram. Iron given orally seems beneficial.

*Vesical outlet obstruction* is frequent in prostatic carcinoma, generally occurring rather late in the disease. Obstructive symptoms often respond to hormonal or antihormonal therapy, but surgical intervention is sometimes necessary. Transurethral resection of the prostate is almost always the choice, regardless of the tumor's size. No attempt is made to remove all the tumor, and resection is necessarily limited. However, the surgeon attempts to remove all obstructing tissue at the vesical neck or within the prostatic urethra. Occasionally, even though resection was adequate, tissue regrows into the prostatic urethra and obstruction occurs, necessitating a second transurethral resection.

When transurethral resection cannot be done, usually a suprapubic cystostomy tube or urethral catheter must remain in place to drain the bladder.

When pain is so severe that it cannot be controlled by other methods, such procedures as presacral rhizotomy and chordotomy are sometimes used.

Besides the foregoing, the usual supportive treatment used in any malignancy is indicated. Good diet, plenty of rest and, especially, good rapport between physician and patient are probably as important as any more specific therapy.

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# The Radiographic Characteristics of Carcinoma of the Prostate

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The recognition of metastases stemming from a primary prostatic carcinoma has significance in two ways: First, it helps in determining the stage to which the disease has progressed which in turn allows us to predict its final prognosis. Second, it helps in determining the type of care best for the patient.

In this paper, we propose to summarize and illustrate known radiographic characteristics of prostatic metastases.

Radiologists recognized prostatic bone metastases as long ago as the turn of the century. Pfahler[10] in 1917 contrasted prostatic carcinoma with osteoarthritis of the spine. He noted both the osteolytic and osteoblastic forms of prostatic metastases. In 1922 Bumpus[6] reported findings from a study of 646 Mayo Clinic patients with prostatic carcinoma. Of these, 228 were examined radiologically with 30 per cent revealing definite metastases in the bones.

Since that time, numerous authors have discussed the x-ray findings associated with carcinoma of the prostate.[7, 9, 11, 13, 14]

## Material

Our case material was drawn from the patient populations of 13 Veterans Administration Hospitals, all participating in a study conducted cooperatively by the National Institute of Health in conjunction with the Veterans Administration. This cooperating group, organized in 1960, has accumulated data on 2781 prostatic cancer patients, all of whom are to be followed and evaluated periodically over an indefinite period for the purpose of judging the effectiveness of various therapeutic techniques and agents.

We have selected our illustrations from 131 patients who entered this

Supported by the Veterans Administration Cooperative Urological Research Project.

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study in a Stage IV condition and who subsequently died. Stage IV is defined as a condition of advanced metastases.

### Techniques for Detecting Metastases

In studying our patients, we used a bone survey which included pictures of the pelvis along with the upper femora, anteroposterior and lateral lumbar spine and thoracic spine, and posteroanterior chest films. At times we have radiographed most of the bones of the body in an attempt to locate unusual sites of metastases. However, we are convinced that the above views are sufficient for detecting early the vast majority of Stage IV bony metastases.

The kilovoltage setting is important in successfully detecting osteoblastic metastases. If the kilovoltage is either too high or too low, the osteoblastic metastases may be obscured or rendered undetectable. The ordinary diagnostic kilovoltage range we have found to be optimum, making certain that all bones are penetrated.

Oblique views, tomograms, coned views and pressure coned views may prove helpful at times, but only in special or questionable cases.

## RADIOGRAPHIC CHARACTERISTICS OF METASTATIC LESIONS

### Histopathology Related to Radiographic Changes

In looking at prostatic metastases histologically we see that the carcinomatous cells invade the venous sinuses of the bone and multiply in the marrow. It has been postulated that one or more factors including chemical, pressure or toxic effects of the carcinomatous cells lead to a hyperemia of the bone-forming elements that results in a reactive growth of the endosteum (Fig. 1). This leads to an increase in the number and thickness of trabeculae on the endosteal side of the cortex, the bone marrow being replaced eventually by trabeculated bone. Occasionally, the osteoclastic action of the bone elements predominate. This results in a radiolucent defect followed occasionally by either of two possibilities: The bone may fracture at the point of metastases, or the bone may be stripped of its periosteum by the invading cells. This results in the formation of periosteal new bone and a widening of the bone (Fig. 2). If the carcinomatous cells do not cause a marked increase in the osteoclastic or osteoblastic response of the bone, then the carcinomatous cells may extensively invade the intertrabecular spaces and avoid radiographic detection and identification as metastases.[3]

### General Appearance of Metastatic Lesions

There are three x-ray types of prostatic bony metastases. Of the 131 patients 99 had definite bone metastases. Seventy-nine had pure osteoblastic type, 12 had mixed lesions, 4 had pure lytic lesions. Three at first

showed demineralization followed by osteoblastic metastases. The one remaining patient had periosteal new bone formation as the only evidence of metastases.[4] Five were suffering from combined endosteal and periosteal metastases, while 76 of the 99 demonstrated diffuse metastases (Fig. 3).

Other sites of metastases were seen in the 131 patients. Pulmonary metastases were observed in 10 per cent of our group (Fig. 4). Five of the 131, or 3.8 per cent, showed neither elevated acid phosphatase or bone metastases and had soft tissue metastases to the viscera or lymph nodes. Twenty-six per cent had an anemia with the hemoglobin below 10 grams per 100 ml. of blood.[2] While the liver showed metastases in 4 per cent of our group, 7 per cent of the patients had metastases to the adrenals. Finally, 6 per cent showed metastases to some part of the central nervous system.

As mentioned above, there are three x-ray types: osteoblastic, osteolytic and mixed, the osteoblastic type being far the most common. Osteoblastic metastases have two usual forms, the first being a fairly sharply demarcated oval density, and the second a poorly demarcated, sheetlike whiteness. When afflicted with this osteoblastic type, the bones rarely increase in size since this new bone proliferation usually occurs inside (endosteal) rather than outside (periosteal) of the bone.

The mixed type usually begins with osteolytic lesions generally unrec-

Figure 1

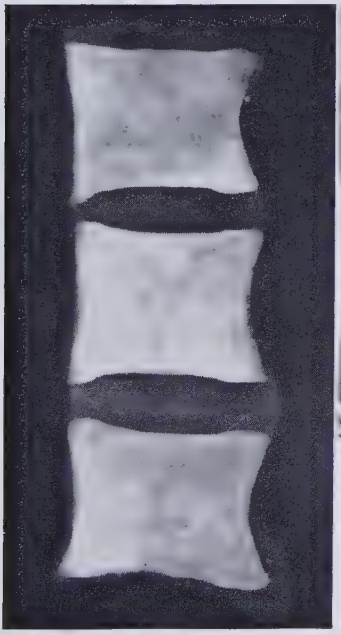

Figure 2

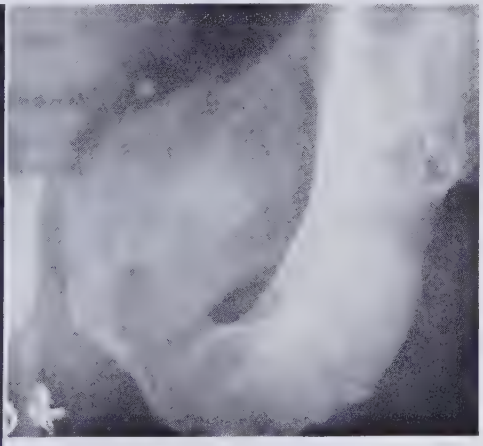

Figure 1. Mottled osteoblastic metastases from the prostate associated with loss of normal trabecular pattern. Autopsy specimen.

Figure 2. Periosteal new bone laid down secondary to pathological fracture of the pubis due to prostatic metastases.

Figure 3

Figure 4

Figure 3. White ribs due to diffuse osteoblastic metastases from the prostate.
Figure 4. Diffuse lymphatic type of metastases in the lung.

ognized as such. Later, there is a superimposition of osteoblastic bone formation. This causes alternating radiolucent and radiopaque areas heterogeneously scattered with no specific pattern (Fig. 5).

The osteolytic type of metastases appears radiographically as a radiolucency caused by a relative absence of bony tissue. This form of metastases is more difficult to detect than the osteoblastic type, especially if it is irregular and poorly marginated or is not invading compact cortical bone. It should be pointed out that a slight general demineralization of a bone may represent diffuse osteolytic metastases almost impossible to recognize radiographically.

We found that metastatic lesions originating from the prostatic carcinoma are most often seen in the pelvis, lumbar and dorsal spine, upper femora, ribs, scapula and upper humeri. This distribution has been verified by many authors.[1, 5, 9, 13]

### Size of the Lesion

The size of the lesion as observed in our material is found to be extremely variable. A homogeneous osteoblastic metastasis measuring 3 mm. in size was detected in the ischium and other bones in which there was not too much superimposition of confusing soft tissue shadows (Fig. 6). The lesions are usually noted to begin with a slight thickening of the trabeculae, eventually coalescing to form a solid density which continues to grow in a more or less symmetrical pattern, much like a nodule growing in the lung (Fig. 7). When small lesions are detected, they tend to be sharply circumscribed rather than appearing as a slight increase in the

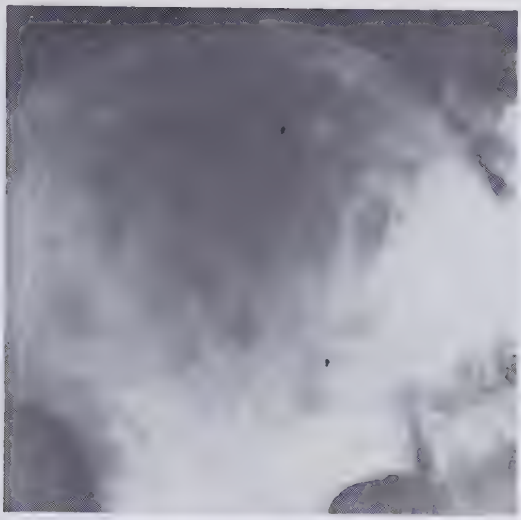

Figure 5. Osteolytic and osteoblastic metastases.

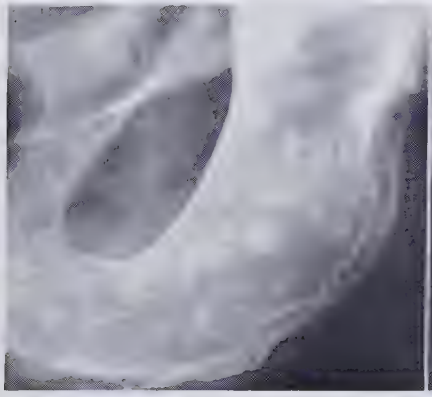

Figure 6

Figure 7

Figure 6. Note the small size of the osteoblastic metastases.
Figure 7. Typical osteoblastic nodules.

trabeculation of the bone and having an irregular border. The detection of a small metastatic bone lesion becomes less likely as the thickness of the patient increases. It is probable that lesions of 1 to 1.5 cm. in diameter may have to be present in the vertebra in order to be detected.

## REGIONAL METASTASES AND THEIR DIFFERENTIAL DIAGNOSIS

### Pelvic Metastases

Osteoblastic metastases in the pelvis are most apt to be recognized in the early, small, spheroid stage in the ischium and in the central portion

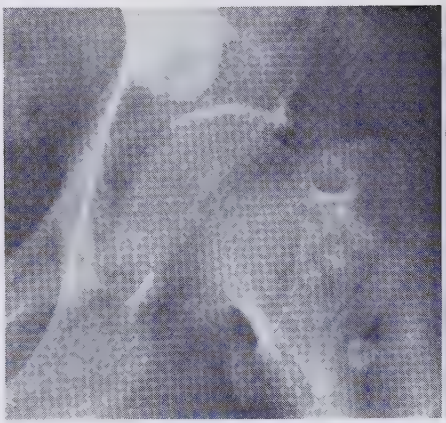

Figure 8

Figure 9

Figure 8. Osteoblastic lesions of varying sizes.
Figure 9. Spheroid and sheetlike prostatic metastases in the ilium.

of the ilium (Figs. 8 and 9). Recognition of osteoblastic metastases is most difficult in those areas normally having increased trabeculation and sclerosis. These areas are found about the sacroiliac joint, the crests of the ilium, the oblique sclerotic line through the lateral portion of the ilium, and subcortical area of the superior margin of the acetabulum.

Certain types of arthritis may simulate or obscure pelvic osteoblastic metastases. One is sacroiliac arthritis; another is arthritis between the fifth lumbar vertebra and first sacral segment. In sacroiliac arthritis we see narrowing and irregularity of the sacroiliac joint and sometimes bone spurs. In arthritis of the hip we often find increased sclerosis and/or cystic changes in the area juxtaposed on the superior acetabular cortical line. These may lead one to presume the existence of a metastatic lesion. In order to be sure, we look for further evidence of hip arthritis, such as a narrowed joint, before making a firm diagnosis.

Another problem area is the crest of the ilium, which normally shows coarsening of the trabeculae. An early osteoblastic lesion superimposed on these areas of sclerosis may be almost impossible to detect. Also in the crest we find new bone proliferation, exophytic changes having to do with aging, or nonspecific inflammation, all of which add to our difficulty in early recognition.

There are two other areas commonly having heavy sclerosis. The first one occurs just below the sacroiliac joint along the inner rim of the pelvis and is triangular in shape. The other runs obliquely from the superior acetabulum toward the upper, outer margin of the ilium. Again, metastases may be superimposed upon these sclerotic areas, making them difficult to recognize.

The central portion of the ilium is seldom involved in the early stages of metastases. The reason for this is not apparent (Fig. 9). On strontium-85

bone scanograms, this area is less active metabolically, which may be an explanation. In the area of the symphysis of the pelvis, we often find sclerotic and cystic changes caused by previous inflammatory processes (Fig. 10), but irregularity of the subchondral bone and the narrowing of the symphysial interspace differentiates this arthritic type of sclerosis from that associated with metastases. However, the possibility that the two may coexist still remains. We also know that rarely do metastases induce joint narrowing through cartilaginous destruction.

Although the sacrum is often involved, we have encountered some difficulty in detecting early lesions in this bone. This is usually due to overlying gas. This problem, however, can be overcome by using a pressure cone technique or minimized by using planigraphy (Fig. 11).

As mentioned above, spur formation or sclerosis associated with intervertebral disk degeneration between the fifth lumbar and first sacral segment often simulates metastases of the upper sacrum. A different projection such as the Fergusson view of the pelvis usually makes this differential diagnosis possible.

In contrast to the osteoblastic form, osteolytic lesions can best be seen in the heavily trabeculated areas of the pelvis. In the central radiolucent area of the ilium osteolytic lesions are difficult to recognize. Around the sacroiliac joint, hip joint and symphysis, metastatic osteolytic lesions have to be differentiated from the arthritic cystic changes mentioned above. Congenital scalloping of the sacral contour is occasionally misinterpreted as metastatic erosions.

Paget's disease gives the appearance of both osteoblastic and osteolytic metastases though it most often simulates the osteoblastic form. In this disease, the bones of the pelvis may become more plastic, resulting in femoral protrusion into the acetabulum. Paget's disease is characterized by coarsening or accentuation of the trabeculae, comparable to the osteo-

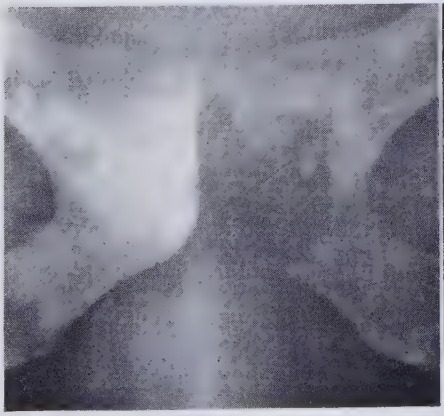

Figure 10

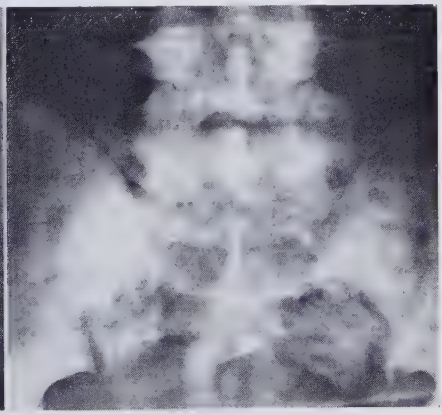

Figure 11

Figure 10. Osteoblastic and osteolytic metastases about the symphysis pubis.
Figure 11. Advanced mixed form of prostatic metastases in the sacrum.

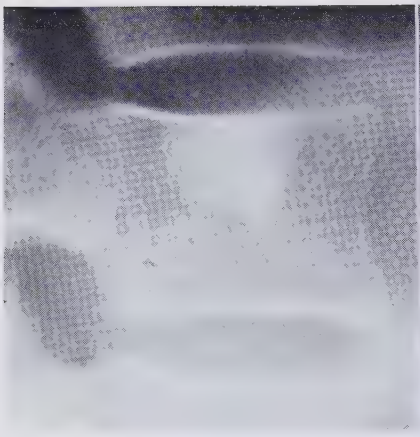

Figure 12

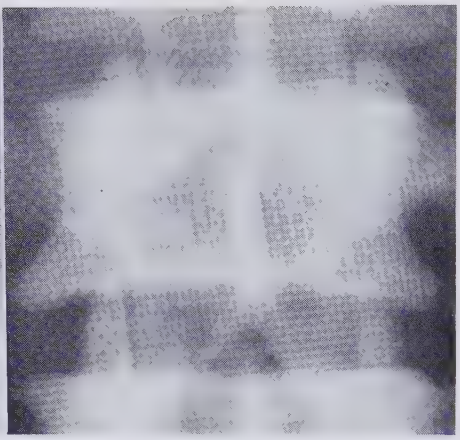

Figure 13

Figure 12. A typical osteoblastic metastasis abutting upon the superior plate and having a sharply demarcated rounded lower margin.

Figure 13. A homogeneous white vertebral body due to prostatic metastases.

blastic form, accompanied by an increase in the width of the bone itself. As Paget's disease appears in the same bones as does prostatic metastases, it cannot be differentiated by location.[12]

**Vertebral Metastases**

The typical vertebral lesion abuts upon a cortical line and has a rounded inner margin (Fig. 12). A more common lesion appears as an area of sclerosis involving one-fourth or more of the vertebral body and having a hazy, poorly demarcated margin. Often in more advanced lesions the entire vertebral body is sclerotic (Fig. 13). Rarely is there any increase in the size of the vertebra. The vertebra is occasionally mottled and sometimes fractured with a resulting loss of height (Fig. 14, *A*, *B*).

An obviously osteolytic lesion is only occasionally seen. It may leave the cortical line intact, and therefore only decreased trabeculation reveals its presence. It is known that minor radiolucent defects in the bone associated with metastases occur but go unrecognized.

The transverse and spinal processes of the vertebra are involved in advanced cases, but metastases in them are more difficult to recognize at an early stage. Again, in the case of the posterior spinous processes and the transverse processes, the thinness of the bones may handicap the early detection of increased density in these parts. Sclerosis of the pedicle is more commonly seen.

Small, round, osteoblastic lesions 1 cm. in diameter can be detected without difficulty in the vertebral body itself. The intervertebral disk spaces are seldom narrowed or widened by metastases since prostatic metastases do not cross zones of cartilage.[4]

Paget's disease of the spine, a fairly common entity among the elderly,

is characterized by an enlargement of the entire vertebra with corresponding accentuation of the trabeculae. In the early stages the vertebral body may appear striated and demineralized, but later it may acquire a large, solid, ivory appearance. The pathological growth of the vertebral body takes place mostly in an anteroposterior and lateral direction, rather than in an increase in the height of the body.

Arthritis of the spine must be differentiated from vertebral metastases. Arthritis of the apophyseal joint shows narrowing, irregularity, spurring, possibly fusion, and sclerosis of the adjoining bone. Again we point out that metastases almost never involve the cartilage of a joint or of an intervertebral space. Degenerative disk disease may lead to sclerosis of the adjoining superior and inferior plates. Sometimes we see a nonspecific sclerosing inflammation involving the anterior portion of the inferior plate of the vertebral body which has resulted in a localized vacuum phenomenon of the adjacent disk. When we have spurring, a localized vacuum, or a slight invagination of the disk into the vertebral plate, we credit the sclerosis to an inflammatory process rather than metastases.

We should note that spurs arising from a vertebral body may overlap the body and can cause a radiographic density which looks like metastases. The offending spur, however, can be distinguished and identified on another projection such as the 90-degree view.

Lymphoma presents a distinct problem in differential diagnosis as it may be associated with increased sclerosis of the vertebra, particularly of a lumbar body, with no increase in bone size. The younger age of the patient, a biopsy specimen, or other clinical findings may be the only clue to the diagnosis of lymphoma.[15]

Occasionally metastases from other organs such as the male breast may be osteoblastic in nature.

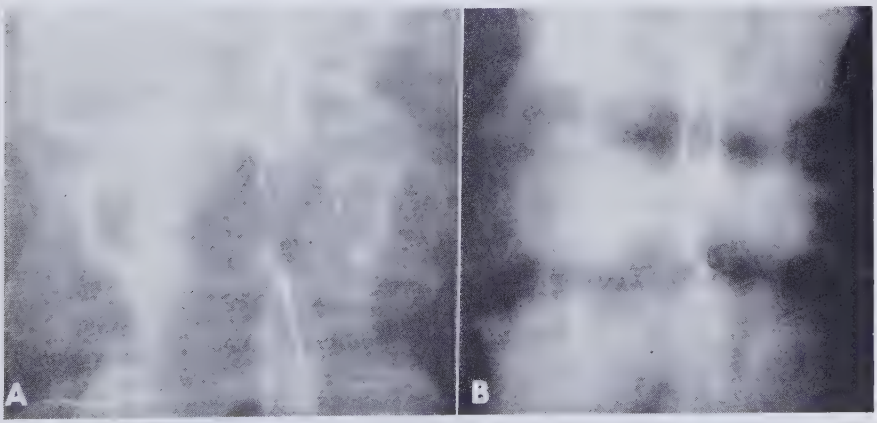


Figure 14. *A*, A normal trabeculated vertebra with minimal old compression deformity. *B*, One year later. Mottled osteoblastic prostatic metastases with considerable compression of the vertebral body.

## Metastatic Lesions of the Ribs

Although we detect various forms of metastatic rib lesions on a routine chest film, some are more readily seen than others. The location of the lesion also plays an important part. For instance, an early osteoblastic metastatic lesion can best be seen in the axillary portion of the rib due to the lack of confusing overlying shadows. If the osteoblastic lesion is sharply demarcated and moderately dense, it can be recognized elsewhere in the rib cage (Fig. 15, *A*). We find that using an oblique view or occasionally an overpenetrated film helps to detect and verify these lesions. All ribs are subject to metastatic lesions of this type, as are all parts of each rib with the exception of the costal cartilage.

One may become aware of rib metastases in a number of ways. A sclerotic lesion of the medullary canal abutting on the cortex usually is the earliest lesion to be recognized. A rib fracture may be secondary to neoplasm. A rib growing in size and increasing in density may result from the stripping of the periosteum from the bone by a growing subperiosteal metastatic lesion (Fig. 15, *C*). Osteolytic lesions of the ribs are recognized much less often than osteoblastic lesions (Fig. 15, *B*). Finally, metastases in the tenth, eleventh, and twelfth ribs are occasionally brought out well in abdominal films.

The radiographic differential diagnosis of diffuse osteoblastic metastases in the ribs can be difficult.[8, 16] A radiographic picture of it gives very much the appearance seen in myelosclerosis or osteopetrosis. The

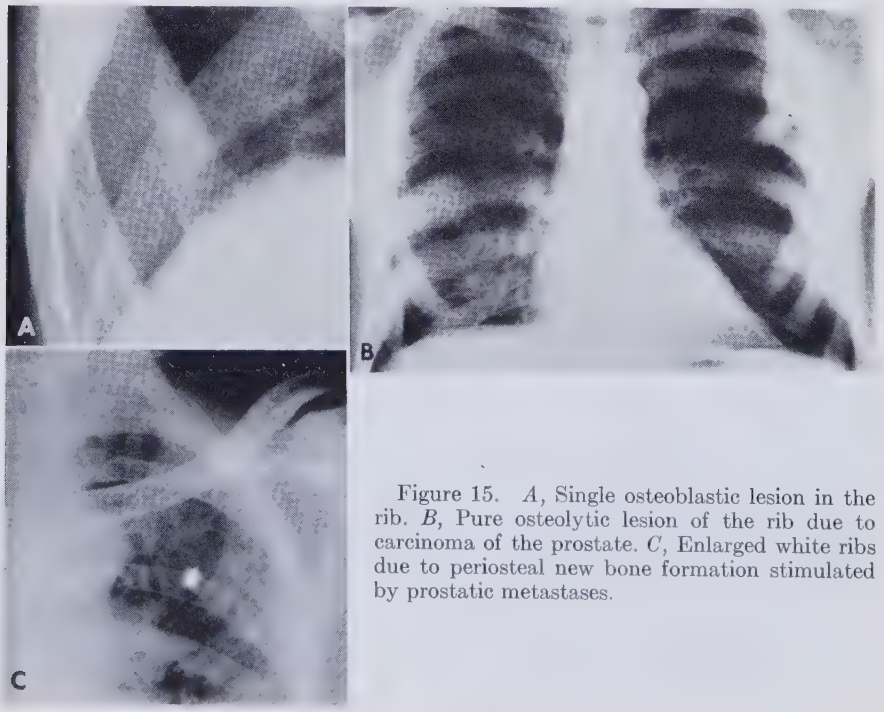


Figure 15. *A*, Single osteoblastic lesion in the rib. *B*, Pure osteolytic lesion of the rib due to carcinoma of the prostate. *C*, Enlarged white ribs due to periosteal new bone formation stimulated by prostatic metastases.

peripheral blood may show evidence of some form of anemia or leukemia in these conditions. Occasionally the spleen is enlarged.[16] Lymphoma also may appear in a radiograph to be similar to osteoblastic metastases. However, if the ribs show diffuse osteoblastic lesions and the patient is a male past 65 years of age, the most probable radiographic diagnosis is prostatic carcinoma.

Multiple myeloma often causes a diffuse demineralization of the ribs interspersed with patches of normal bone, making a mottled picture. Care must be taken that this mottling effect not be misdiagnosed as osteoblastic metastases.

Old fractures of the ribs, per se, can usually be differentiated through the presence of multiple fractures in a single vertical plane. We usually have a history of trauma in these cases in addition. Occasionally an osteoma, originating from the endosteum, may pass as a metastatic lesion. However, the fact that there is only one and it fails to grow with the passage of time aids in this differential diagnosis.

Paget's disease usually enlarges the affected ribs and therefore is not difficult to differentiate from metastases. Only rarely does an osteolytic or a sclerotic form of Paget's disease without increased rib size occur to confuse the observer.

### Metastatic Lesions of the Shoulder

Metastases in the area of the shoulder are frequently seen. Lesions are found along the lateral margin of the scapula, the neck of the scapula and in the coracoid process (Fig. 16). We also find that metastases in the

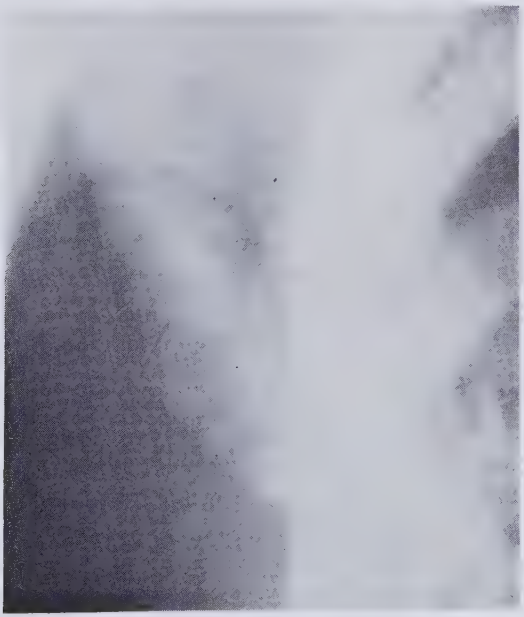

Figure 16. Mixed form of metastases in the scapula.

Figure 17. Osteoblastic metastases in the femur.

proximal humeri are relatively common and not difficult to recognize. Occasionally we see metastases in the clavicle. Other sites may have metastases, but we find difficulty in recognizing them owing to superimposition of overlying structures.

Paget's disease can be found in all the bones of the shoulder and is differentiated again by the characteristic increase in the size of the affected part. Here, as in other bones, Paget's disease may show either coarsening of the trabeculae or a completely sclerotic, white appearance.

**Metastatic Lesions of the Upper Femur**

We find metastases to be usually osteoblastic in type in the upper femoral area (Fig. 17). The head, neck and intratrochanteric portions of the upper end of the femur are generally involved. The lesions shows either a sheetlike appearance, coarsening of the trabeculae or the typical ivory-like effect previously mentioned. Bone islands of the neck must be differentiated from the spheroid type of carcinomatous lesion, again by its singularity and lack of growth as observed over a period of time. Also, Paget's disease has its peculiarities in this area. It does not enlarge the head or neck of the femur, since a lack of periosteum makes it impossible for periosteal bone to form, thus making differentiation difficult at times. If there is simply coarsening of the trabeculation, it may be impossible to differentiate an early lesion, but, as a general rule, metastases to the upper end of the femur are round, oval or sheetlike in character, different in appearance from Paget's disease. If, by chance, we have the sclerotic form of Paget's disease in its advanced state in the head and neck of the femur,

it can be differentiated from metastases by the typical appearance of the femoral shaft with its periosteal new bone proliferation, coxa vara deformity, and anterolateral bowing of the shaft. Lymphoma of the bone is also found in the femur as well as the pelvis, ribs and vertebrae and must be differentiated by other clinical findings as it is extremely hard to differentiate radiologically. Fortunately, only about 5 per cent of lymphomas show blastic lesions.

There are distinct areas other than those already mentioned where prostatic metastases may occur. In general, they include the bones of the knee and elbow joints and the vault of the skull. The midshafts of long bones tend to remain free of prostatic carcinoma while the highly metabolic and vascularized areas about the joints are more prone to attack. Bone of the hands and feet are usually involved only when the disease is diffusely spread throughout the body.

## SUMMARY

Our experience has shown that over 78 per cent of prostatic metastases are of the pure osteoblastic type. Seldom do we find a pure lytic lesion or periosteal new bone formation alone. Bone islands, Paget's disease, some form of lymphoma, nonspecific osteitis, and nonspecific myelosclerosis of the bones must be considered differentially.

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# Management of Benign Prostatic Hypertrophy

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Benign prostatic hypertrophy frequently is present in the aging male. However, in many instances no treatment is indicated for this condition. By referring to five specific indications for surgical intervention, unnecessary treatment may be avoided.

The term benign prostatic hypertrophy is used here because of its common clinical acceptance. Although there is disagreement concerning the exact etiology, development and terminology of this condition, this is of no significance to the practicing physician. Benign prostatic hypertrophy consists of periurethral masses composed of glands and fibromuscular tissue. This tissue is frequently referred to as the prostatic adenoma and it compresses the true prostate to the periphery. This adenoma usually occurs as two lateral lobes, a median lobe, or a combination of all three lobes. Rarely an anterior lobe is present.

## INDICATIONS FOR THERAPY

The five indications for therapy are residual urine, symptoms, bladder changes, other states adversely affected by increased intra-abdominal pressure and uncontrollable hemorrhage. The size of the prostatic adenoma plays no part in the decision as to whether or not treatment is indicated. Some adenomas can reach a large size without causing trouble while others which are quite small can cause complete urinary retention.

### Residual Urine

Residual urine of 75 cc. or more perhaps is the strongest indication for the need of intervention. This represents early decompensation of the bladder and alerts the physician to the possibility of progressive difficulty. Urinary tract obstruction with residual urine provides a fertile field for

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urinary tract infection. Once established it is most difficult, if not impossible, to eradicate infection in the presence of urinary stasis. The figure of 75 cc. is not a rigid one and may be modified somewhat by other factors. If a patient has a persistent urinary tract infection with attacks of cystitis operation is considered when a smaller amount of residual urine is present. On the other hand, a residual urine of 100 cc. is occasionally permitted if there is no infection and the patient otherwise is doing well. Residual urine may be evaluated by several methods.

1. The *catheter* is the most accurate means of determining the amount of residual urine. Complete urinary retention, with or without overflow, is interpreted as a residual urine. When complete retention is not present it is necessary to catheterize the patient immediately after voiding. The discovery of 125 cc. of urine in the bladder of a patient who cannot void is not an indication of residual urine. If a catheter cannot be passed, or if it is not desirable to do so, residual urine may be ruled out by other means. However, if any of these other methods fail to rule out a residual urine a catheter should be used if at all possible.

2. The *air test* is simple and is done easily in the office. A patient is taken at a time when he feels that he will be able to void. The patient lies on the examining table and the glans penis is cleansed. The tip of a bulb syringe is wedged into the urethral meatus and approximately 40 cc. of air is injected into the bladder. One can determine the moment the urinary sphincter relaxes and allows the air to enter the bladder, for there will be a diminution of pressure in the rubber bulb of the syringe at this time. The patient then stands to void. As the urine is expelled the air remains in the most superior portion of the bladder. It does not escape until after the urine has been eliminated. The sound of air passing per urethra will not be mistaken and will rule out residual urine.

3. *Post-voiding x-ray films* may be used to evaluate residual urine. A radiopaque aqueous solution is introduced through the penis with a bulb syringe and the patient asked to void. An x-ray film of the bladder then is taken. A post-voiding film may be taken in conjunction with an intravenous pyelogram provided that the patient is able to void and there is sufficient contrast material in the bladder for adequate visualization. X-ray determination of residual urine lacks popularity because of the comparative costs involved.

4. The *phenolsulfonphthalein test* is occasionally used for determining the presence of a residual urine. The phenolsulfonphthalein test gives one an indication of overall renal function. When used properly it also gives information concerning stasis in the urinary tract. After adequate hydration a patient is given an intravenous injection of 1 cc. of phenolsulfonphthalein measured in a 1-cc. tuberculin syringe. The urine is collected every 30 minutes for two hours, care being taken that each entire specimen is saved. For a satisfactory test 100 cc. or more must be collected each 30 minutes. The highest concentration of dye should be present in the first 30 minute

specimen. If a higher concentration is present in a later specimen this is known as a delayed peak and indicates residual urine. As a rule of thumb, the 30-minute specimen will contain at least one-half of the total two-hour excretion unless residual urine is present.

**Symptoms**

Nocturia of three or more times from benign prostatic hypertrophy is an indication for treatment. Lower urinary tract obstruction causes a number of signs and symptoms. Although these do not progress in any consistent order, the first sign usually noted is diminution in the size and force of the urinary stream. Hesitancy in initiation of urinary stream and straining to void are frequently the first hints that therapy may be required. Occasionally double voiding is seen. This arises when the bladder muscles become fatigued before the bladder is empty. After a rest of a few minutes enough strength is regained to force out an additional amount of urine. Often a sensation of incomplete emptying of the bladder is noted. Increased resistance to urinary outflow requires a higher intravesical pressure to initiate voiding and hypertrophy of the detrusor muscle occurs. This, in turn, causes increased irritability of the muscle so that a smaller amount of urine in the bladder gives rise to the desire to void. Urinary frequency and ofttimes urinary urgency is the result. Frequency in benign prostatic hypertrophy also is seen when a residual urine is present, and, thus, the functional capacity of the bladder is reduced.

Frequency is caused by other factors which must be taken into consideration. An acute urinary tract infection is usually recognized and must be corrected before evaluation of this symptom can be made. Occasionally frequency is caused by a bladder tumor or foreign body. Some patients experience urinary frequency and urgency because of nervous tension. Because of this, the amount of nocturia is of great importance. Patients with nervous tension usually will not be awakened by the desire to void once they have gone to sleep. Patients with frequency because of urinary tract obstruction will be awakened by the desire to void. Nocturia of three or more times is sufficient to warrant surgical intervention. The nocturia of benign prostatic hypertrophy is not characterized by the voiding of large quantities of urine. However, polyuria from uncontrolled diabetes mellitus or from diabetes insipidus will cause nocturia in a patient with a normal voiding mechanism. Similarly, nocturia may be seen in a patient in congestive heart failure when fluid is pooled in the body during periods of activity only to be eliminated by a nocturnal diuresis. This can be overlooked in instances of early failure. An accurate method of obtaining facts concerning nocturia is the recording of individual voidings. To do this a record is maintained of the time and volume of each voiding. By examination of this record the patient with nocturia but with large urinary output is discovered.

### Bladder Changes

The presence of bladder diverticula formation or impending formation from prostatic obstruction is an indication for operation. As the detrusor muscle does more work to overcome the increased resistance of the prostatic urethra, muscular hypertrophy results. This is seen through the cystoscope as trabeculation. As voiding bladder pressure increases, further small protrusions of the mucosa are seen between the hypertrophied muscle fibers and are known as cellules. The final stage of change is diverticula formation in which the cellules enlarge and extend beyond the bladder wall. These diverticula have no effective muscle in their walls and thus harbor residual urine. Intervention should be made before these changes have progressed to diverticula formation. The appearance of the prostatic urethra through the endoscope is not in itself an indication for surgery. It is not rare to find a gland that appears to be obstructing the urethra by endoscopy but does not lead to the presence of criteria for therapy. One must determine from history and examination whether bladder changes may be the result of a urethral stricture which has been relieved. Prostatic surgery is not indicated in such a case.

### Hernia or Hemorrhoids

Prostatic obstruction should be treated when increased intra-abdominal pressure is required for voiding which adversely affects other diseases or body conditions that are present. The two most common examples of these are hernia and hemorrhoids. Prior to herniorrhaphy it should be determined whether or not it is necessary for the patient to strain to void. If this is required lower urinary tract obstruction should be corrected, for any increase in intra-abdominal pressure will make the herniorrhaphy less likely to succeed. The same principle applies to the patient for hemorrhoidectomy.

### Hemorrhage

On rare occasions it is necessary to enucleate a prostatic adenoma to control bleeding. This is seen almost entirely in the very large adenoma in which all efforts fail to stop massive hemorrhage. The bleeding is often precipitated by urethral instrumentation or an infarction in the prostate. By removal of the adenoma the physician is able to leave the patient with a relatively smooth and viable lining of the prostatic fossa. Under these circumstances bleeding is more readily controlled.

### Diseases Other Than Benign Prostatic Hypertrophy That Can Give Similar Findings

Even when one of the five indications for treatment does exist the physician still must consider if this could be produced by a disease or condition other than benign prostatic hypertrophy.

A urethral stricture can cause obstruction leading to bladder changes, residual urine, frequency, nocturia and urgency. Following relief of the stricture, bladder changes often linger. Often benign prostatic hypertrophy coexists with a stricture. In this instance, the stricture must be treated and then the patient re-evaluated for benign prostatic hypertrophy.

Neurogenic bladder with residual urine may be present without obvious neurological signs, as is sometimes seen in pernicious anemia or diabetes mellitus.

Carcinoma of the prostate can cause urethral obstruction or it may be present in a gland in which the benign prostatic hypertrophy is causing the obstruction. Carcinoma of the prostate should be treated for at least two weeks before an operation is considered on the prostate for obstruction. Under hormone therapy the carcinoma will frequently shrink enough to relieve the obstruction. Even when shrinkage is not this complete the surgeon is left with a smaller gland for surgery.

Bladder irritation with frequency, urgency and nocturia is also present with acute infections, bladder tumors or foreign bodies in the bladder.

A patient with borderline urinary compensation can be pushed into retention by administration of drugs such as atropine and Pro-Banthine in the treatment of ulcer disease. Effective voiding often can be restored by discontinuing the drugs.

Retention can occur when a patient becomes debilitated by a serious illness or operation or whenever the bladder is allowed to become overdistended.

## PREOPERATIVE EVALUATION AND PREPARATION

Surgery is the only definitive treatment for benign prostatic hypertrophy. After the need for therapy has been established it is determined whether or not this surgery may be done.

A *blood urea nitrogen* determination is made to evaluate overall renal function. An elevated blood urea nitrogen may be secondary to lower urinary tract obstruction or to chronic, irreversible, renal parenchymal changes. The patient with residual urine and azotemia is treated with an indwelling catheter. The blood urea nitrogen is redetermined at weekly intervals until it returns to normal. Following the relief of chronic urinary retention the patient must be observed for excessive sodium diuresis. If the blood urea nitrogen stabilizes at an elevated value an operation still may be considered. However, a constant value above 40 mg. per 100 ml. of blood is a poor prognostic sign and surgery is contraindicated.

An *intravenous pyelogram* reveals the status of the upper urinary tract. Following longstanding prostatic obstruction hydronephrosis and hydroureter are frequently seen and are treated with an indwelling catheter prior to operation. Most instances of hydronephrosis secondary to benign pros-

tatic hypertrophy will disappear following two to three weeks of bladder drainage.

*Anemia* when present with benign prostatic hypertrophy is frequently related to an elevated blood urea nitrogen or to infections in the urinary tract. Before surgery the hemoglobin level should be raised to 13 grams or more. This may be done by removing the cause of anemia or by transfusion.

An *indwelling catheter* is indicated for an elevated blood urea nitrogen or hydronephrosis and in the presence of a large residual urine in an attempt to allow the bladder to regain its normal tone. An indwelling catheter is not needed always in instances of less than 200 cc. of uninfected residual urine provided that surgical intervention is planned in the near future. However, a catheter must be used if infection is present. Antimicrobial therapy is used with the preoperative retention catheter.

*General medical evaluation* of the patient is made, as is usual in other surgical candidates, to evaluate the anesthetic risk. Cardiovascular disorders as well as hemorrhagic tendencies are particularly important.

## CHOICE OF OPERATION

At this point in the evaluation the type of surgery to be performed is determined. The choice here is between a closed prostatectomy (transurethral resection) and an open prostatectomy. This is based primarily upon the size of the prostatic adenoma. This size is first determined by rectal palpation which is done with the bladder empty. A distended bladder can force the prostate downward in such a manner as to cause the size of the adenoma to be overestimated. A transurethral resection is performed if the surgeon thinks that he can remove the adenoma in one hour or less with a resectoscope. This amount of tissue will vary somewhat according to the skill of the resectionist but will usually be 50 grams or less. A transurethral resection should not be prolonged over one hour because of the possibility of excessive absorption of fluid from the prostatic fossa causing water intoxication and sodium diuresis. Prolonged cutting time during a transurethral resection also allows an extended time for bleeding to occur from the adenoma. Transurethral resection of the prostate is carried out in patients with coexistent, incurable carcinoma of the prostate regardless of the size of the prostate. A cystoscopy is done immediately preceding the transurethral resection to evaluate any bladder disease that may be present. A bilateral vas ligation lowers the incidence of postoperative epididymitis.

If the prostate feels large on rectal examination the patient is further evaluated by endoscopy for open surgery. At the same time the bladder is examined. Unless the adenoma is found to be large by both rectal examination and endoscopy an open prostatectomy should not be done. Open prostatectomy is best done when there is a well developed cleavage plane between the adenoma and the true prostatic tissue. This plane is poorly

developed in small prostates and is often destroyed in patients with prostatic carcinoma. These patients should be treated by transurethral resection. Coexisting bladder disease requiring surgry allows open prostatectomy to be considered in a patient with a smaller prostate than is usually removed by open operation.

If open prostatectomy is chosen for the patient the surgeon must then decide upon his approach. The three most common procedures are suprapubic prostatectomy, retropubic prostatectomy and perineal prostatectomy. The choice between these is primarily a matter of individual preference. The suprapubic prostatectomy is the easiest performed and allows surgery to be performed upon the bladder. The retropubic prostatectomy requires more operating time but allows hemostasis under direct visualization. The length of hospitalization in retropubic prostatectomy is shorter than in the other two open operations. The perineal operation is the least frequently used because there are few operators with adequate experience in working in the perineum. The distressing complications of urethrorectal fistula and incontinence turn many away from this approach. Bilateral vasectomy is done with open prostatectomies to lower the incidence of postoperative epididymitis.

## COMPLICATIONS OF SURGERY

Incontinence can follow any type of surgery but decreases as the skill of the operator increases. The incidence is highest following transurethral resection and perineal prostatectomy but may follow an attempted suprapubic enucleation of a small adenoma.

Secondary hemorrhage is not rare in any of the operations but is more frequent following transurethral resection. This usually occurs between 7 and 14 days postoperatively and in most instances is easily managed with evacuation of bladder clots followed by an indwelling catheter for one to two days.

Impotence is most common following perineal prostatectomy and is seen least with transurethral resection. However, retrograde ejaculation frequently is seen following transurethral resection and this should be explained to the patient prior to discharge.

Urethral stricture is a hazard of transurethral resection, and perforation of the bladder with extravasation of urine is a complication solely of this procedure.

Osteitis pubis occasionally is seen following retropubic prostatectomy but on rare occasions had been reported after a transurethral resection.

Urethrorectal fistula is seen almost exclusively with perineal prostatectomy and may be quite difficult to correct.

Pyuria will follow all prostatectomies and patients are placed on antimicrobial treatment for at least two weeks.

If patients are chosen for operation on the basis of the five indications given above the surgeon may expect to have a high success rate following the properly chosen operation.

## SUMMARY

Benign prostatic hypertrophy is seen frequently but often does not require therapy. The five indications for treatment are residual urine, symptoms, bladder changes, conditions made worse by increased intra-abdominal pressure, and uncontrollable hemorrhage. Surgery is the only definitive treatment but is not done when the patient is uremic or anemic. The size of the prostate determines whether a transurethral resection or an open prostatectomy is done. Complications of surgery are incontinence, secondary hemorrhage, impotence, urethral stricture, osteitis pubis and urethrorectal fistula.

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# Prostatitis

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Clinically, prostatitis can be classified as acute or chronic. A special category is established for granulomatous prostatitis. Terms such as congestive and stromal infiltration will be ignored.

The prostate prior to puberty is barely palpable to the examining finger. Inflammations of the organ at this age are extremely rare, only occasionally occurring when associated with congenital anomalies of the lower urinary tract or prolonged catheter drainage. The prostate matures during the puberal period as a result of testosterone stimulation. Rectal examination reveals a smooth, symmetrical organ which does not project into the rectum. Its texture is slightly resilient and of a rubbery consistency. There is a division of the lateral lobes with a central groove. One can generally get above and to the side of the prostate with the examining finger unless the patient is markedly obese. Pressure upon the prostate is normally unpleasant and gives the sensation of the desire to urinate. It is slightly mobile on examination of the lateral portions (Fig. 1). The posterior surface is usually three fingerbreadths from side to side, and about two and one-half fingerbreadths in length; in other words, approximately 3.5 by 2.5 cm. The seminal vesicles are not palpable normally. When massaged, several drops of opalescent fluid will usually be obtained. Examination of the fluid under the microscope reveals only occasional white blood cells and no bacteria. Round fragments a bit larger than white blood cells called lecithin bodies are found in abundance.

## ACUTE PROSTATITIS

Acute prostatitis is clearly caused by bacterial invasion of the prostate. The organisms involved vary, the commonest being Escherichia coli and Staphylococcus aureus. They enter the prostate either through embolic deposition from the blood stream or by direct extension of infection from

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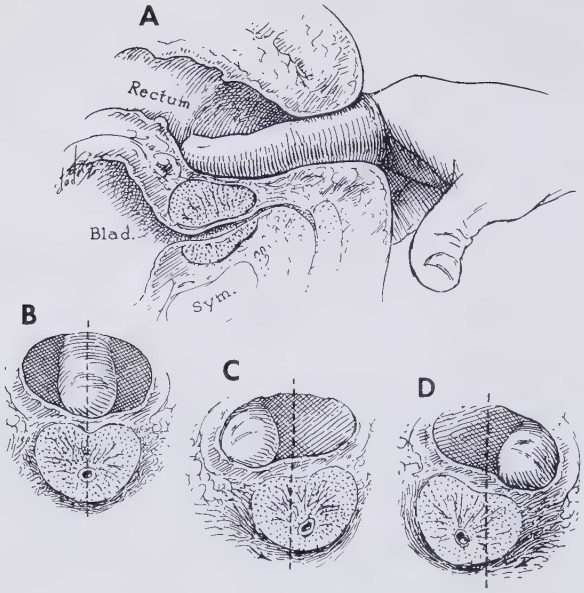


Figure 1. Position and size of normal prostate illustrating its mobility.

the posterior urethra. It is most commonly secondary to chronic urethritis and is associated with urethral manipulation such as occurs with an indwelling catheter.

Specific acute prostatitis due to gonorrhea is less common since the advent of antibacterial drugs, but is still occasionally seen.

The symptoms and signs of acute prostatitis are those of infection. Chills and fever with pain in the abdomen, perineum or rectum will occur. There may be an associated urethritis and urethral discharge. Often the discharge of the products of infection into the urethra is noted, causing cloudy, purulent urine. Urination is frequent, in small amounts and is painful. The prostate is surrounded by a tough, fibrous capsule and, as a result of acute swelling, voiding may become difficult. Occasionally, there is complete retention of urine. Rectal examination will disclose an enlarged, acutely tender prostate. If microscopic abscesses have coalesced, digital examination will reveal a firm, bulging mass. The division of the lateral lobes usually disappears owing to swelling and edema. There can be considerable asymmetry with one lobe greatly larger than the other. If draining through the urethra has begun, the abscessed area may be soft with indurated edges. There actually can be a depression in the surface contour where the abscess cavity is located. The prostate is acutely tender and it is difficult to examine. The seminal vesicles may well be engorged and sensitive as a result of obstruction and infection. X-ray examination will reveal the bladder neck to be elevated. The intravesical portion of the prostate is not surrounded by a capsule and acute swelling will tend to enlarge in

this direction. Massage should not be carried out during the acute phase because of the possibility of spreading the infection into the blood stream or to the epididymi. Fluid will frequently be obtained if there is a draining abscess, and it is filled with the cells of acute inflammation. The fluid is obviously purulent, contains no lecithin bodies, and is filled with bacteria.

The complications of acute prostatitis are prostatic abscess, urinary retention, bacteremia, epididymitis and pyelonephritis. The treatment consists of bed rest, adequate diet and appropriate antibacterial therapy. The complications must be treated as they occur. Prostatic abscesses will usually drain spontaneously through the urethra. Operative drainage through the urethra or perineum occasionally is necessary. Urinary retention is treated with a small urethral catheter. In the presence of a severe urethritis, suprapubic cystostomy may be the appropriate method of drainage of the bladder. Epididymitis will generally respond to conservative management, and only occasionally requires drainage or epididymectomy. Manipulation of the urethra and rectal examination should be minimized during the acute process except for diagnostic purposes in order to minimize these complications.

The diagnosis is not difficult but careful evaluation should be made to rule out acute inflammatory processes in adjacent organs; for example, acute appendicitis or acute diverticulitis. Either may cause acute pelvic inflammation in men, and it is particularly important that the differential diagnosis in these cases be made early.

## CHRONIC PROSTATITIS

Chronic prostatitis is a clinical syndrome comprised of: (1) symptoms relating to the prostate; (2) minimal physical findings; (3) usually normal urine, and (4) variable findings on rectal examination of the prostate. The cause of chronic prostatitis is unknown. There are undoubtedly some cases which are a residual of an acute prostatitis, although usually this history is unobtainable.

There are two types of prostatic secretion; one a more or less continuous secretion of small amounts of fluid which collects in the glands and ducts, and from time to time is discharged into the posterior urethra and bladder. Upon appropriate stimulation, the prostate in animals can develop a high secretory pressure, and in a relatively short period of time secrete a volume greater than the gland itself. The second type of secretion occurs with ejaculation and includes not only an emptying of the glands and ducts by muscular contraction, but actual rupture of acinar cells into the lumina of the glands. It has been demonstrated in animals that almost complete denudation of the epithelium occurs after repeated copulations. This accounts for the presence of intracellular enzymes within the seminal fluid and it is logical that under these circumstances the gland is more

susceptible to inflammations. Associated with some edema and obstruction of the glands, it is reasonable that these sophisticated proteins, originally present in the glandular epithelium, might well extravasate into the periglandular tissue causing an inflammatory reaction without the presence of pathogenic bacteria. Many bacteria have been implicated, and bacteria are frequently cultured from the prostatic fluid of these patients, but no direct causal relationship has been established. It may well be that they are essentially nonpathogenic.

The symptoms ascribed to this entity somewhat in the order of frequency are as follows:

1. The patients complain of urethral discharge which is seldom demonstrable at the time of examination but is more commonly noted upon arising in the morning.

2. They complain of difficult voiding, frequency and dysuria.

3. Pain may radiate to the tip of the penis, to the perineum or to the scrotum.

4. They also have symptoms referable to other parts of the body, for example, low back pain, and groin pain radiating to the genitalia.

The history and physical examination may elicit other inflammatory illnesses such as arthritis or iritis. There are frequently sexual symptoms of an inadequacy of one sort or another. The patients may complain of general symptoms such as loss of weight or appetite, and nervousness. The urine is usually normal although some shreds may be noted, particularly in the first portion voided. Examination may reveal a large, boggy prostate (Fig. 2). It is sometimes normal to the examining finger. There may be some areas of nodularity, particularly in the upper portions of the gland. The prostate is not particularly tender, and the patient will submit quite readily to prostatic massage. The secretion collected following massage is usually greater in volume than in the normal state, being from 1 to 5 cc. Microscopic examination of the prostatic fluid will reveal numerous pus cells per high power field.

Chronic prostatitis is related to several situations which should be borne in mind when planning the treatment of these unfortunate persons. For example, those patients who are sexually inadequate and constitutionally asthenic will complain oftener and consult their physicians more frequently. It has been the observation of most that similar physical findings are frequently found in apparently normal men in whom these rather minor and physiologic changes do not concern the patient enough to see a physician. There is a clear clinical relationship between this syndrome and benign prostatic hypertrophy and other obstructive diseases of the posterior urethra and bladder neck. This should be borne in mind while treating these patients, so that they can be given the benefit of the treatment of obstructive bladder neck disease.

Chronic prostatitis is associated with other inflammatory diseases such as arthritis and iritis. The prostate has long been considered a focus of

infection, and in fact, a causative factor in these other entities. Likewise, the reverse has been proposed from time to time, namely, that inflammatory conditions of the prostate may be secondary to bacterial foci elsewhere in the body; for example, infected teeth or tonsils. Since we have minimized the role of bacteria in the cause of chronic prostatitis, it would be unreasonable to state that the bacteria present in these distant organs cause an exacerbation of prostatic inflammation. More likely, there are proteins present within the epithelium of the prostate which are common to other specific organ systems. With intermittent experience with these proteins, the body learns to recognize them as foreign when they escape the acinar epithelium, occasionally causing inflammations in other organs where they are encountered, as synovia or the iris of the eye. This, then, would logically explain the frequently noted observation that arthritis and iritis associated with prostatitis are exacerbated by massage of the prostate gland. It may well be that benign prostatic hypertrophy is a tissue response to such an inflammatory reaction recurring locally over a period of many years.

The treatment of chronic prostatitis consists of a careful history and physical examination, careful examination of the genitalia and prostate, and reassurance. The patient should be assured that he does not have a serious disease and that it is not venereal in nature. This is especially

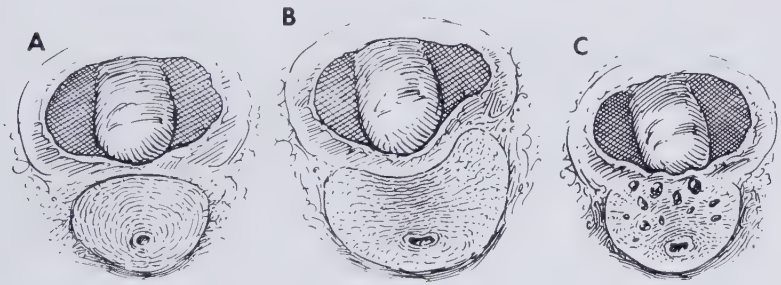


Figure 2. Rectal Findings in Chronic Prostatitis

*A*, The prostate that is firm and fibrotic. It develops induration early, particularly at the base of the gland near the seminal vesicles, frequently causing nodularity which suggests malignancy. Later, this may involve the entire gland. The prostate is normal to small in size and is frequently associated with prostatic calculi. The seminal vesicles may become thickened and apparent on rectal examination. Prostatic fluid is difficult to obtain unless there is a concomitant benign prostatic hypertrophy.

*B*, Soft, boggy prostate. The consistency is pillowy. There is an increase in size of the prostate and usually decreased tenderness is present. Prostatic fluid is abundant (3 to 5 cc.) and contains clumps of white cells. This condition is apparently caused by dilation of the prostatic acini with little interstitial fibrosis.

*C*, Calculous prostatitis. The size may vary as it is frequently associated with benign prostatic hypertrophy. Stones may be single or multiple and lie in any portion of the gland. If they are adjacent to each other, there may be crepitation. When associated with a benign adenoma, they are usually found between the adenoma and the posterior capsule of the prostate and are therefore easily palpable. In the absence of crepitation, they may be confused with carcinoma. X-ray examination of this area is therefore helpful.

important because in much of our western culture it has been impressed upon the individual that venereal disease is a tragic thing. This early attention makes a special impression on sexually and psychically inadequate persons. A sense of well-being is frequently attained by occasional gentle prostatic massage. This reduces the pressure within the prostate on a very temporary basis. Antibiotics usually have little effect except from a placebo standpoint.

## GRANULOMATOUS PROSTATITIS

Granulomatous prostatitis was first described in 1943.* The histologic picture is of a chronic, inflammatory and foreign body type tissue reaction which suggests that this inflammatory reaction was caused by extravasation of the products of the acinar epithelium into the interstitial tissue. The disease presents following a febrile episode, frequently associated with obstructive symptoms and pyuria. The prostate is firm, hard and asymmetrical. The findings mimic carcinoma and require a tissue sample for exact diagnosis. Management includes relief of the obstructive symptoms and treatment specifically of any secondary bacterial involvement. The condition is self-limiting, and the prostate reverts in a matter of months to a more normal gland on palpation.

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# Acid Phosphatase in Urology

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Phosphatases are a large group of enzymes which hydrolyze a variety of phosphate esters and phosphate anhydrides (pyrophosphates and metaphosphates). The phosphate esters may be classified as (*a*) phosphomonoesters, (*b*) phosphodiesters and (*c*) phosphotriesters. At the present time only (*a*) and (*b*) are known to be constituents of vertebrate cells. Only the phosphomonoesterases have been widely studied. A somewhat arbitrary but useful subclassification has been to distinguish the phosphomonoesterases as to whether they have pH optima in the acid range (acid phosphatase) or in the alkaline range (alkaline phosphatase). Acid phosphatases have been described in highest concentration in the cells and secretion of the prostatic gland. They are also found in erythrocytes (two enzymes described), urine, kidney, liver, spleen, pancreas, bile, bone and serum. In addition, small amounts of acid phosphatase have been described in small intestinal mucosa, cerebrospinal fluid, saliva, amniotic fluid, esophagus, stomach, colon, rectum, skeletal and heart muscle, breast, bronchus, skin, bladder, thyroid, adrenal, brain and in leukocytes and platelets and perhaps in all cells at one time or another in their life span.

Increased clinical interest followed the description of acid phosphatase in the tissue of prostatic cancer metastases[20] and the subsequent description of elevated serum acid phosphatase levels in such patients.[3, 18] This interest was intensified by the demonstration that the decrease in serum acid phosphatase following therapy with orchiectomy or estrogens generally was paralleled by a decrease in pain and a decrease in the size of the primary

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Supported in part by the Veterans Administration Cooperative Urological Research Project and U. S. Public Health Grant CA-05113-03S1.

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and metastatic lesions.[22, 25, 46] Remission following adrenalectomy has also been associated with a decrease in serum acid phosphatase.[24] A continuing intensive series of attempts subsequently have been made to develop methodology suitable for the specific measurement of prostatic serum acid phosphatase. These attempts in general have followed two lines of investigation: a search for a substrate specific for the prostatic enzyme and a search for differential inhibitors which would either inhibit the nonprostatic acid phosphomonoesterases or specifically inhibit the prostatic enzyme. These attempts have to date met with only partial success. Unfortunately, many of the leading investigators have made significant modifications in the methods which they have used and frequently the method has come to be named after the investigator who utilized it. This has resulted in a large number of acid phosphatase methods with different names and units. Most methods have one or more unique features which prevent their values from being interchangeable with values obtained by one of the other methods. An understanding of methodology is, therefore, basic to an understanding of the field.

## METHODOLOGY

### Specificity of Common Acid Phosphomonoesterase Substrates

PHENYL PHOSPHATE. This substrate is used in the King-Armstrong method.[33] A King-Armstrong unit is that amount of enzyme which will liberate 1 mg. of phenol per hour from phenyl phosphate at pH 4.9. Modifications have been used by Gutman and Gutman[19] and Benotti, Rosenberg and Dewey.[4] Use of this substrate with measurement of the liberated phosphate rather than the liberated phenol was the basis of a method by King, Abul-Fadl and Walker.[32] This substrate is nonspecific and is hydrolyzed by acid phosphatase of most tissues. However, utilization of inhibitors such as L(+)-tartrate has greatly increased its usefulness (*vide infra*).

β-GLYCEROPHOSPHATE. This substrate is used in the Bodansky method.[6] A Bodansky unit is that amount of enzyme which will liberate 1 mg. of phosphorus per hour from β-glycerophosphate at pH 4.9. This substrate was originally used by Martland,[39] then Kay,[29] Jenner and Kay,[28] Bodansky[6] and Herbert.[22] Modifications were subsequently described by Hawk, Oser and Summerson;[21] Shinowara, Jones and Reinhart;[44] and Woodard.[48] The necessity for measurement of serum phosphorus before and after hydrolysis gives these methods a high blank and limits their reproducibility. This substrate is more specific than phenyl phosphate since it is not hydrolyzed by erythrocyte acid phosphate to any appreciable extent. However, hepatic, renal and splenic acid phosphatases have not been systematically studied and elevations in liver disease sometimes prove troublesome.[48]

PARA-NITROPHENYL PHOSPHATE. This substrate is used in the

Bessey-Lowry method.[5] A Bessey-Lowry unit is that amount of enzyme which will liberate 1 mM. of para-nitrophenol per hour at pH 4.9. This substrate was used first by Ohmori[40] and King and Delory,[34] and subsequently utilized by Hudson, Brendler and Scott,[23] and Jacobson.[27] Liberated para-nitrophenol has an absorption peak at 410 mμ whereas the substrate absorption peaks at 230 mμ and does not absorb at 410mμ.[5] A direct reading of absorption change at 410 mμ following hydrolysis can, therefore, be made without addition of a color reagent. This substrate is hydrolyzed by both erythrocyte and prostatic acid phosphatases.

Phenolphthalein Phosphate. This substrate is used in the Huggins-Talalay method.[26] One unit is that amount of enzyme which will liberate 0.1 mg. phenolphthalein per hour at pH 4.9. This substrate was first used by Bray and King.[5] It is also hydrolyzed by both prostatic and erythrocyte acid phosphatase.

β-Naphthyl Phosphate. This substrate is used in the Seligman method.[43] One unit is that amount of enzyme which will liberate 10 mg. of β-naphthol per hour at pH 4.9. The method requires protein precipitation and an extraction step with ethyl acetate. It has been criticized because some of the azo dye remains bound to the precipitated protein.[2] This substrate is also hydrolyzed readily by both erythrocyte and prostatic acid phosphatase.

α-Naphthyl Phosphate. This substrate is used in the Babson-Read method.[2] One Babson-Read unit is that amount of enzyme which will liberate 1 mg. of α-naphthol per hour at pH 5.2. This substrate is highly specific for prostatic acid phosphatase when compared to erythrocyte acid phosphatase. However, hepatic, splenic and renal acid phosphatase have not been tested and elevation in chronic hepatitis has been noted.

### Specificity of Phosphomonoesterase Inhibitors

L-Tartrate. In an extensive and incisive investigation of phosphomonoesterase inhibitors, Abul-Fadl and King[1] found that 0.01 M L(+)-tartrate inhibited 95 per cent of the activity of the prostatic acid phosphatase enzyme but none of the erythrocyte activity. Only the L(+) form was active as an inhibitor and so the D(−) form and racemic mixtures should be avoided. Fishman and Lerner[16] utilized a phenylphosphate substrate with a measurement of acid phosphatase activity with and without L(+)-tartrate inhibition. The difference of the two measurements then represented "tartrate inhibitable" serum acid phosphatase activity which in the usual instance represented prostatic acid phosphatase activity especially when elevated. However, Abul-Fadl and King[1] noted that acid phosphatase activity from liver, kidney and spleen was also 70 to 85 per cent tartrate inhibitable and so it might be anticipated that occasional instances of elevation of tartrate inhibitable serum acid phosphatase will represent instances of hepatic, renal or splenic disease.

The original method of Fishman and Lerner utilized the Folin-

Ciocalteau reagent for measurement of released phenol but this necessitated the precipitation of plasma proteins before the color measurement could be done.[16] Subsequent modifications for phenol measurement have included use of an amino-antipyrine condensation reaction which does not require prior precipitation of plasma proteins.[31] This method of phenol measurement is sensitive and reproducible. Increased absorbancy can be obtained by moving from the usual wavelength used (580 mμ) toward the maxima at 500 mμ.

Jacobsson[27] has attempted to utilize L(+)-tartrate inhibition with para-nitrophenyl phosphate as a substrate utilizing a pH of 5.5. He recognized the warning of Fishman and Davidson that L(+)-tartrate is not an efficient inhibitor of prostatic acid phosphatase when para-nitrophenyl phosphate is used as a substrate.[15] Jacobsson has shown apparent 97 per cent inhibition of the enzyme from a prostatic extract. However, his values show an excessively high total to "tartrate inhibitable" ratio when the method is applied to serum or plasma. In addition, an increased risk of alkaline phosphatase "cross-over" is present. Demonstration that no interference occurred in one case with elevated alkaline phosphatase is not reassuring since a variation in optimal pH has been demonstrated in the family of alkaline phosphatase enzymes.

FORMALDEHYDE INHIBITION. Abul-Fadl and King reported 100 per cent inhibition of erythrocyte acid phosphatase but no inhibition of prostatic enzyme with 0.5 per cent formaldehyde.[1] Acid phosphatase from other sources was inhibited 12 to 60 per cent. Theoretically the two common major acid phosphatases of blood could be distinguished in this manner without need of a subtraction step. However, elevation of serum acid phosphatase from hepatic, renal or splenic sources would still increase the non-formaldehyde inhibited (prostatic) fractions. This approach has not found wide use possibly because it has no clear advantage over tartrate inhibition.

ETHYL ALCOHOL INHIBITION. Kutscher and Worner[36, 37] first described the irreversible inactivation of prostatic acid phosphatase by certain narcotics, including alcohols. Herbert[22] used this inactivation as a means of identifying prostatic acid phosphatase in serum and attempted clinical utilization of these facts. However, King, Wood and Delory[35] and Herbert[22] noted inactivation of erythrocyte acid phosphatase under the conditions (30-minute incubation) shown for inactivation of serum prostatic acid phosphatase. Abul-Fadl and King[1] noted 70 to 80 per cent inhibition of erythrocyte acid phosphatase by ethyl alcohol under conditions giving 90 to 100 per cent inhibition of prostatic acid phosphatase and so this approach would appear to lack specificity. However, it is of value to note that hepatic and splenic acid phosphatase are not inhibited by ethyl alcohol and so absence of inhibition with ethyl alcohol could have differential diagnostic significance when combined with other methods.

HEAT INACTIVATION AT 37° C. Kutscher and Worner[37] noted that prostatic acid phosphatase was destroyed by incubation at 37°. Herbert[22]

found 92 to 97 per cent inactivation of prostatic juice acid phosphatase added to serum with heating to 37° for one hour at pH 7.4. Almost complete stability at 37° was found at a lower pH. Heating was advanced as a method for adding to the specificity of the prostatic acid phosphatase determination. No decrease in activity on heating was felt to be strong confirmation of a normal value but a drop on heating was not necessarily confirmation of an elevation due to prostatic enzyme. Woodard[48] showed that female serum acid phosphatase and hepatic acid phosphatase had a similar heat lability.

Preservation of Acid Phosphatase. It is essential that the conditions of collection, transport and storage of serum prevent any deterioration of acid phosphatase activity. Destruction of prostatic acid phosphatase at room temperature is pH dependent (Fig. 1) with greatest stability at pH 6.2. Prostatic acid phosphatase can be preserved at room temperature through the use of a solid disodium citrate buffer prepared in a pre-weighed tablet form* (Fig. 2). The prostatic acid phosphatase was also preserved well for at least one week by refrigeration at 5° or freezing at −15° C. The blood should be refrigerated immediately after venipuncture, the red cells separated from the serum as soon as possible and the serum brought to pH 6.2 and refrigerated and the assay performed at the earliest possible time. It should be emphasized that erythrocyte acid phosphatase is not

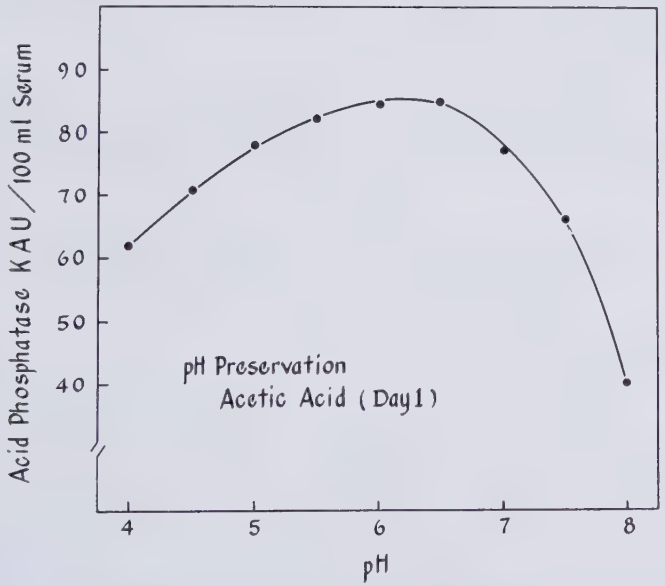


Figure 1. Optimal preservation of serum acid phosphatase at 25° C. at pH 6.2. The value at day 1 was slightly higher than the enzyme concentration determined immediately. (Method utilized phenyl phosphate substrate pH 4.9 with aminoantipyrine color development of the released phenol. (KAU = King-Armstrong Units.)

* Disodium citrate supplied by General Diagnostics Division of Warner-Lambert, Inc. (one 18-mg tablet added per cubic centimeter of serum).

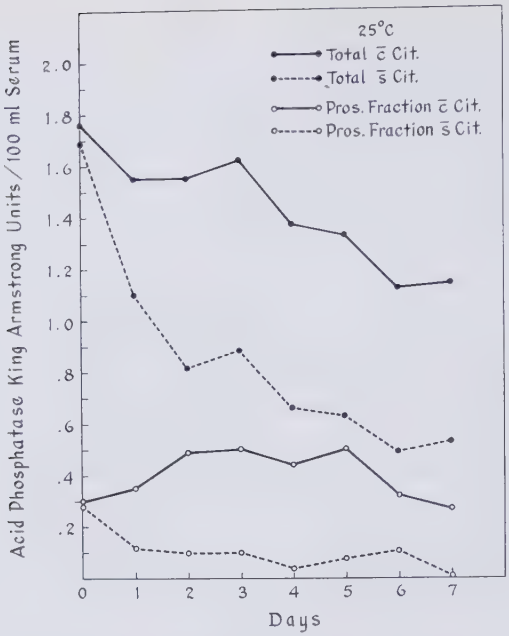


Figure 2. Use of disodium citrate tablets for preservation of prostatic acid phosphatase (same method as Fig. 1) in 14 normal subjects. The elevation in tartrate inhibitable acid phosphatase was significant at day 2 ($p < .02$) as was the drop in both fractions without citrate at day 1 ($p < .01$).

preserved adequately under these conditions and so methods which measure both erythrocyte and prostatic acid phosphatase will not show similar preservation.

## CLINICAL MEANING OF CHANGES IN SERUM PROSTATIC PHOSPHOMONOESTERASE

### True Elevations

A true serum elevation of the enzyme requires a change in the equilibrium between production, release into the blood stream, inhibition and destruction. It is sometimes claimed that an elevation in serum acid phosphatase concentration is evidence of tumor extension past the prostate capsule. This is possibly true on the mean, but the correlation must be far from perfect. Some of the reasons for this are readily apparent. Undifferentiated cell types will sometimes be incapable of acid phosphatase production. Chance location of a tumor in a blood vessel wall will allow its secretion to be more evident than otherwise possible in terms of elevation of serum acid phosphatase concentration. The mechanism for destruction of the enzyme is unknown, but in some subjects the catabolic process may be deficient (possibly in hepatic disease).

With this as a background, the difficulties in correlating extent of tumor with degree of elevation of serum acid phosphatase become apparent. Table 1 details the acid phosphatase findings in patients with carcinoma of the prostate. In each series approximately 60 per cent of the prostatic cancer patients had elevations in serum acid phosphatase. About 80 per cent of those with bony metastases had elevated acid phosphatase levels. Perhaps more significantly this means that 20 per cent of those with bony metastases had normal serum acid phosphatase levels. Herbert, for instance, had six patients in the latter category. One patient proved to have very undifferentiated carcinoma on biopsy. Another patient eventually developed a serum acid phosphatase elevation when terminal and so some potential to produce acid phosphatase had existed from the start. Of those without bony metastases, the number with elevated serum acid phosphatase was quite variable but averaged about 30 per cent. Woodard found that 5 per cent of patients with cancer localized to the prostate have elevated serum acid phosphatase levels.[49] The number of patients with localized or distant soft tissue metastases, of course, cannot be detected from the latter method of reporting. Cook, Fishman and Clark[9] noted no patients with cancer localized to the prostate to have elevations, 47 per cent with local pelvic soft tissue metastases to have elevations, 87 per cent with bony metastases to have elevations, and 100 per cent of those with distant soft tissue metastases without bony metastases to have elevations. This series, therefore, has the best correlation between extent of tumor and serum acid phosphatase concentration of any reported.

Woodard and Dean[50] found that all but 10 per cent of patients with an elevated serum acid phosphatase had a clinical remission with hormonal

**Table 1.** *Reported Incidence of Abnormal Serum Acid Phosphatase Concentration in Patients with Metastatic Prostatic Cancer*

| REFERENCE | NO. PTS. | NO. ELEV. | NO. WITH BONY METASTASES | NO. ELEV. | NO. WITHOUT BONY METASTASES | NO. ELEV. |
|---|---|---|---|---|---|---|
| Huggins and Hodges (1941) | 47 | 21 | 25 | 19 | 20 | 1 |
| Sullivan, Gutman and Gutman (1942) | 200 | 126 | 130 | 115 | 70 | 11 |
| Watkinson, Delory, King and Haddow (1944) | 10 | 6 | 7 | 6 | 3 | 0 |
| Smith and McLean (1943) | 10 | 7 | 5 | 3 | 5 | 4 |
| Herbert (1946) | 87 | 42 | 35 | 29 | 47 | 12 |
| Woodard and Dean (1947) | 127 | 70 | 71 | 51 | 56 | 19 |
| Cook, Fishman and Clark (1962) | 108 | 63 | 37 | 32 | 71 | 31 |
| TOTAL | 589 | 335 | 310 | 255 | 272 | 88 |

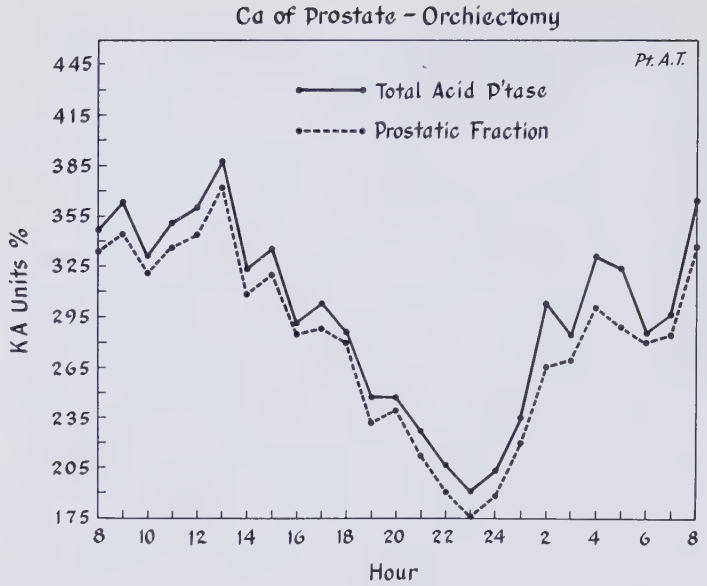


Figure 3. The circadian variation in serum acid phosphatase concentration in prostate cancer persists after orchiectomy. (KA = King-Armstrong.)

therapy and this was associated with a decrease in the serum acid phosphatase. Subsequent relapse might or might not have been accompanied by an increase in acid phosphatase. About 20 per cent of untreated patients experienced an increase in serum acid phosphatase. Serial interpretation of such changes is made more complicated by the marked circadian variation in serum concentration which exists (Fig. 3). The circadian variation persists in spite of removal of the testes, or if the adrenal rhythm is obliterated by 1 mg. of dexamethasone every three hours for 17 days. Since the peak of the circadian variation is not reached at the same clock hour each day, apparent decrease or increase of the serum enzyme concentration may occur if only isolated samples are relied upon in serial studies in patients.[13]

According to Woodard and Dean,[50] patients with prostatic carcinoma have a somewhat decreased concentration of tissue acid phosphatase to begin with (cancer 110 to 500 units/gm.; normal 169 to 1350 units/gm.). Measurement of tissue acid phosphatase in cases in relapse after endocrine therapy showed acid phosphatase concentration to be greatly decreased (5 to 54 units/gm.).

Schenken, Burns and Kohle[41] demonstrated that diethylstilbestrol caused the prostatic cancer cells to undergo regressive changes. The cells became vacuolated in the cytoplasm, nuclei became pyknotic and eventual cellular breakdown, death and replacement fibrosis occurred. Unchanged prostatic cancer cells following estrogen were rare but present. One attractive hypothesis might be the possibility that some of the cancer cells were resistant to hormonal therapy from the beginning and eventually became

the surviving tumor.[17] There is some evidence which would indicate that the surviving cells also have a decrease (on the mean) in ability to elevate the serum acid phosphatase concentration. Woodard and Dean[50] found that of 22 patients with elevated serum acid phosphatase concentration, all decreased with hormonal therapy and 12 failed to reach serum levels as high as the pretreatment concentration upon relapse in spite of having much more cancer tissue present in the terminal phase of their course. As noted above, the acid phosphatase concentration of the cancer cells was much decreased following estrogen. No differences in histology have been identified to date to allow prediction of cells resistant to androgen withdrawal[41] or to differentiate the cells seen in relapse from those present pretherapy.[50]

### False Elevations (Not Due to Prostatic Cancer)

Elevations Following Mechanical Stimulation. Whitmore and Woodard[51] found elevations in serum acid phosphatase following surgery. Bonner, Homburger and Fishman[7] found transient elevation of serum acid phosphatase in 50 per cent of 22 men following rectal palpation. However, Kendall[30] found that elevation following rectal examination was six times more frequent in patients with prostatic cancer than in noncancer controls (32 vs. 5 per cent). Unfortunately, the timing sequence following elevations due to mechanical manipulations of the prostate has not been carefully studied.

Elevations Due to Other Diseases. Occasionally elevations in serum acid phosphatase have occurred in cases of nonprostatic disease in the absence of prostatic cancer. These have been systematized[38] and will not be repeated here. Suffice it to say that if all hepatic, renal or bone disease is eliminated, almost all of the elevations are accounted for. In most instances, the false elevations are mild in degree and frequently disappear if a more specific substrate ($\beta$-glycerophosphate, $\alpha$-naphthol phosphate) or specific inhibitor (L-tartrate) are used. Some of the most persistent and striking elevations have occurred with hepatic disease.[22] In these cases, the enzyme was not inhibited by ethyl alcohol and this is consistent with a splenic or hepatic origin.

## URINARY ACID PHOSPHATASE

Acid phosphatase was first described as occurring in the urine,[12] but the subsequent studies in changes in serum concentration coupled with some technical difficulties in the urinary measurement have pushed the urinary enzyme into oblivion. More recently evidence has been presented which would indicate that measurement of urinary acid phosphatase would aid in the diagnosis of prostatic cancer.[11, 42] Another challenges the usefulness of the urinary measurement.[10]

It must be assumed that in many instances the preponderance of urinary acid phosphatase originates in the kidney because of the finding of tartrate inhibitable acid phosphatase in the renal pelvis in a concentration frequently as high as in simultaneously voided urine,[14] because no correlation exists between serum and urinary acid phosphatase activity in cases of prostatic cancer,[14] and in light of the known fact that renal acid phosphatase is tartrate inhibitable[1] (apparently localized in the proximal renal tubule). The contribution of acid phosphatase from the prostate is at best inconsistent. Urinary acid phosphatase is, therefore, of no value in early diagnosis of cancer of the prostate or in following its response to therapy.[10, 14]

## SUMMARY

1. Methodology has been reviewed which will allow separate measurement of erythrocyte acid phosphatase from the prostatic enzyme. This can be done through the use of the relatively specific substrates such as $\beta$-glycerophosphate, $\alpha$-naphthol phosphate or through use of the nonspecific substrate, phenyl phosphate, combined with use of the inhibitor L(+)-tartrate. Unfortunately, separation of prostatic acid phosphatase from the hepatic, splenic and renal enzymes is not well established. The term "tartrate inhibitable" acid phosphatase is, therefore, superior to the term prostatic acid phosphatase.

2. Prostatic acid phosphatase is well preserved by disodium citrate tablets at pH 6.2 at 25°C. and at 5° and −15°C. This is not true of erythrocyte acid phosphatase or alkaline phosphatase. Freezing to −15°C. preserves the enzyme with or without disodium citrate buffer.

3. The marked circadian variation in serum acid phosphatase makes minor changes (less than 40 per cent) difficult to interpret.

4. Urinary acid phosphatase originates mainly in the kidney and is not of value in the diagnosis or in following the course of therapy in prostatic cancer.

ACKNOWLEDGMENT

The authors wish to thank Miss Mary Miller and Miss Barbara Johnson for aid in preparation of the manuscript.

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# The Pathophysiology of the Urinary Sphincter

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The ability to void at will and maintain urinary continence has a mystique not yet completely dispelled. Gaps of information remain. Nevertheless, by using mechanics, electronics and roentgenology, more is known today about sphincter function than ever before. It is our purpose to call attention to the prevailing winds of concept and some of the common clinical problems encountered, with a sketchy reference to therapy. Our primary focus of interest is function at the sphincetric urethra rather than the bladder.

## ANATOMY

### One Sphincter System, Two Components

Reference to an internal and an external sphincter is giving way to the view of a single sphincter system consisting of a tubular extension of the bladder detrusor[29] with a partial outer coating of striated muscle fibers most concentrated where the tube traverses the urogenital diaphragm. This is the traditional "external sphincter," which lies about 9 mm. distal to the verumontanum (Rolnick and Arnheim) in the male and in the region of the middle or distal third of the urethra in the female, in whom it is much weaker.

In thinner distribution striated muscle may be found as far proximally as the bladder neck and trigone.[5] Both smooth and striated muscle reach deeply into the prostate gland (Beneventi and Marshall, Kost and Evans). There is no iris-like "internal sphincter." An independent muscle structure at the vesical neck cannot be found.[29] In the male the entire prostatic and the membranous urethra make up the sphincter; in the female it is the entire urethra, which is 3 to 4.5 cm. in length (Lapides). The smooth muscle tube contains much elastic tissue,[29] diffuse in the female and most

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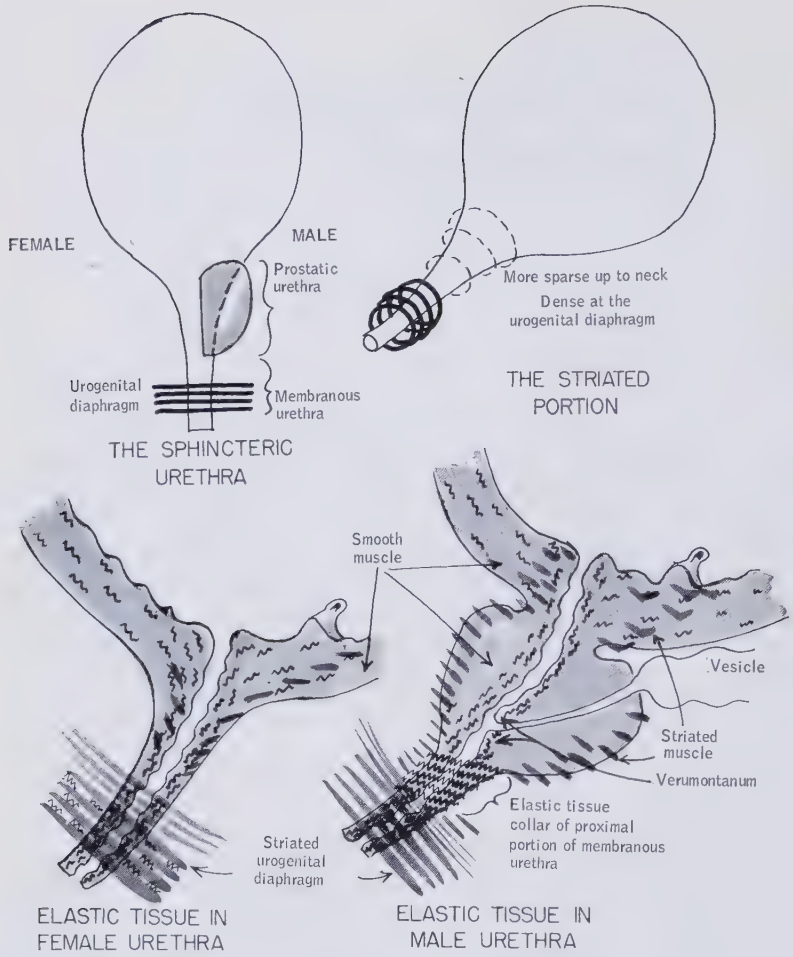


Figure 1. Anatomy of the urinary sphincter.

concentrated in the male at the membranous urethra[22] between the prostatic apex and the urogenital diaphragm.

### The Pelvic Floor and Perineal Musculature

These serve to support the bladder base and urethra in the female and the prostate in the male. The urogenital diaphragm, the ischiocavernosus and bulbocavernosus muscles comprise the perineal group and are closely related to the sphincteric urethra, while the pubococcygeus of the levator ani is the chief element of the hammock-like support.

### Pertinent Nerve Supply

The striated musculature of the pelvic floor and perineum is supplied by sacral somatic outflow chiefly via the pudendal nerves. The detrusor's

parasympathetic supply also takes origin in the sacral segments and reaches the bladder via the pelvic nerves. Both outflows can be damaged by lesions at the conus or cauda equina. The sympathetic system supplies fibers to the smooth muscle of the bladder neck,[6] trigone and genital adnexa, and in the male is important only in the sphincter's role in sex function.

## NORMAL PHYSIOLOGY

### The Mechanism of Voluntary Micturition

Based on the work of Denny-Brown and Robertson in 1933, one view, supported by Lapides and others, asserts that the detrusor can be contracted or relaxed voluntarily to start or stop micturition. The striated musculature of the pelvic floor and perineum is considered unessential though providing an expeditious cutoff of the stream in interruption of micturition. The other theory expressed chiefly by Muellner denies that smooth muscle can be controlled voluntarily. According to this view, micturition consists first of a somatic phase in which the striated musculature is relaxed voluntarily to pull down the bladder neck. This movement secondarily triggers the autonomic reflex detrusor contraction. Voluntary contraction of the striated muscles raises the neck of the bladder and reflexly stops the detrusor contractions.

### Sphincter Changes in Micturition

However one may explain voluntary voiding, these are the observed sequences and changes: At rest the vesical neck is high in the pelvis. On initiation of micturition, the pelvic floor relaxes and the neck drops. The detrusor and its tubular extension contract thereby opening wide the vesical neck. The urethra is foreshortened and the striated portion of the sphincter at the diaphragm relaxes reflexly to allow flow. Electromyographic activity in the striated muscles is absent during this period but returns the instant the muscles are contracted to interrupt micturition by elevating the bladder neck. There is some dispute as to whether the vesical neck or the striated portion of the sphincter closes first and whether the latter can be relaxed voluntarily.

### Continence: Holding One's Water

Passive Continence. Passive or unconscious continence[9] is effortless. It depends upon a sphincteric urethra about 3 cm. or more in length and an intraluminal tension created by the smooth muscle, the elastic tissue, and the tonus of the striated muscle.[29] The manner of suspension of the urethra serves to keep it taut, narrow, of adequate length and at an obtuse angle with the floor of the bladder. The turgor of healthy mucosa aids in coaptation of the urethral surfaces.

Active Continence. Conscious continence[9] requires effort and de-

pends upon voluntary forcible contraction of the striated portion of the sphincter. The muscle fatigues rapidly. A contraction at maximum lasts only seconds[11, 12] while at lower levels it can be maintained erratically for one or more minutes with extreme discomfort. A short rest is required to regain a maximal contraction. The purpose of such brief voluntary contraction is to pinch off the urethra until cessation or inhibition of detrusor contractions is accomplished.

THE FAIL-SAFE MECHANISMS OF CONTINENCE. The striated portion of the sphincter may be held open forcibly, injured[28] or paralyzed without loss of urine if the bladder neck and immediately adjacent urethra remain intact, though there may be slight stress incontinence. Conversely, the bladder neck and immediately adjacent urethra may be injured as in a transurethral resection without involuntary loss of urine if the distal urethra is intact. After radical prostatectomy the membranous urethra and striated portion of the sphincter provide good control with slight stress incontinence in most cases. More remarkable, after simple prostatectomy in which the bladder neck usually becomes incompetent,[9] the striated sphincter portion may be paralyzed as by bilateral pudendal nerve block without escape of urine,[9] emphasizing the effectiveness of the smooth muscle and elastic tissue collar of the male's membranous urethra,[28] but interruption of micturition is delayed.[9] Any sudden increase in intra-abdominal pressure as by coughing, laughing or straining causes a reflex contraction of the perineal and pelvic floor musculature serving to pinch off the urethra long enough to prevent escape of urine. Flaccid injured musculature or loss of this reflex leads to stress incontinence.

CONTINENCE AND STRUCTURAL FACTORS IN THE SEXES. In males the support provided by the pelvic floor and perineal musculature is rarely disturbed and ordinarily not important in incontinence. In females their support is crucial to the maintenance of the urethra at adequate length tautness, narrowness and proper angle with the floor of the bladder. Disruption of this support may result in some degree of stress incontinence.

## The Sphincteric Urethra in Ejaculation

The male urethra conveys seminal fluid as well as urine. The former is propelled into the posterior urethra by smooth muscle contractions of the epididymides, vasa, seminal vesicles, ejaculatory ducts and prostate through sympathetic impulses which also contract the vesical neck and the distal portion of the trigone to create a temporary backstop to prevent retrograde flow of the fluid.[25] A second or somatic phase follows with contractions of the perineal musculature including the striated portion of the sphincter[18] to eject the fluid distally, the bulbocavernosus serving to empty the anterior urethra, a function it also serves at the end of micturition.

A transurethral resection or equivalent mechanical injury to the neck of the bladder results in retrograde flow of semen into the bladder during the somatic phase of ejaculation. Interruption of sympathetic supply as in

presacral neurectomy and sympathectomies is also followed by diminished fluid in the posterior urethra and retrograde[26] flow into the bladder. Sacral cord or cauda equina lesions bring loss of the somatic function. Complete lesions above the sacral cord permit reflex somatic phase ejaculatory function.

## SPHINCTER CHANGES LEADING TO INCREASED RESISTANCE

Bearing in mind the need for balance between the active expulsive and passive resisting forces, the sphincteric urethra must not be abnormally elongated, rigid and immobile, too narrow, or mechanically blocked in any way that will prevent the detrusor from widening the neck, shortening the urethra, and providing adequate lumen. In brief, inability to actively diminish the passive sphincteric resistance means obstruction.

### Obstruction in Infants and Children

In a neurologically normal infant or child, symptoms such as bouts of fever, poor urinary stream, infected urine, erratic, distressed or infrequent voiding, abdominal discomfort, enuresis, residual urine, flank pains, vesicoureteral reflux, dilated upper tracts and deteriorated renal function can be the result of increased sphincteric urethral resistance loosely referred to as bladder neck contracture or bladder outlet obstruction. Recognition that there are two types of such obstruction has cleared up some of the confusion.[20] However, diagnosis is difficult and there are uncertainties of interpretations of some cystourethrographies.[16]

A primary congenital form is characterized by overabundant elastic tissue with abnormal elongation of the urethra, creating great elastic peripheral resistance. Considered rare by some, others feel it may be common but in early stages difficult to detect.[20] A sign of the times is the present frequent use of the terms elastoplasia and fibroelastosis used by Bodian, who in 1957 described the advanced pathology in several male infants, noting that the process involves not the orifice alone but the entire sphincteric urethra.[4]

A secondary type results from an initial localized point of resistance distinctly distal to the bladder neck.[21] Causes include congenital valves in the posterior urethra in the male, congenital fibrotic or spasm rings just beyond the striated portion of the urethra, or bands of tissue, or valvelike flaps of mucous membrane in the distal female urethra, a stenotic meatus or stricture of congenital infectious or traumatic origin in both sexes. Urethrograms show a distended urethra between the neck and the point of obstruction.

In both types peripheral resistance causes hypertrophy of the smooth muscle of the bladder, neck and urethra. This is interpreted as "work response" and in the secondary type is reversible[16] provided fibrous con-

tracture from chronic infection has not occurred before the distal obstruction is eliminated.

Diagnostic procedures include excretion urography, voiding cinecystourethrography, endoscopy and calibration. The elusiveness of the diagnosis in early cases which may show slight or no obvious physical evidences of obstruction[16] has stimulated investigative programs in larger centers employing analysis of combined electronic recording of flow rate and intravesical pressure during voiding. To obtain the latter, fine plastic urethral or suprapubic catheters are used. There is some overlapping of pressure results but the high readings point to obstruction.[16]

TREATMENT. In secondary obstruction this includes urethral dilatations, incision of bands, mucosal flaps and rings in the female and transurethral electroresection or open surgery of posterior urethral valves and urethroplasty for stricture in the male. Meatotomy is done in both sexes. For the fibrotic contracture which may develop in primary and secondary types of obstruction incident to chronic infection and for the muscular hypertrophy itself, electroresection may still be used but cold-cutting methods whether by urethrotome[19] or open operation which may include a Y-V plasty of the neck are advocated to avoid the cicatricial propensities of high frequency current. Related measures include corrective surgery for vesicoureteral reflux when this is required. Lively controversy continues on the etiology and therapy of such reflux. A substantial bulk of the cases appears to be related to sphincteric urethral obstruction.[23] In far advanced deterioration, cystostomy, vesicostomy and nephrostomy may be carried out.

### Obstruction in Adults

Increased resistance appears with massive prostatic hypertrophy which stretches the bladder neck, elongates, angulates and so broadens the urethra in the anteroposterior diameter and encroaches upon its lumen by its bulk as to increase the intraluminal tension while making the vesical aperture rigid and immobile. It may also present as a small type of hypertrophy with a normal neck but a narrow urethra or as a fibrotic contracture secondary to chronic infection of prostatitis, cystitis or stricture, or a previous transurethral resection. Finally there may be a congential contracture described as fibromuscular hypertrophy which began in childhood and links with the older concept of Marion and Bodian's fibroelastosis.

Obstructive resistance also occurs in women but its nature is not as well defined.[10] Congenital fibroelastosis, chronic inflammatory changes with edema, squamous metaplasia, lymphocytic infiltration, fibromuscular hyperplasia, fibrosis, epithelial and gland hyperplasia, normal muscle and connective tissue and some subtle functional disorder have all been implicated. As in males, a previous transurethral resection may be a source of contracture. Increase in the vesicourethral angle may be a cause of obstruction if bladder base and proximal urethra descend.

The basis for symptoms is the resistance to and delay in widening the neck[10] and shortening the urethra and its quick closure[14] with consequent hesitancy, weak unsustained stream, dribbling, decompensation and finally residual urine. Treatment includes enucleation of the hyperplastic prostatic tissue, endoscopic electroresection, or use of cold-cutting methods endoscopically or by open operation which may include a Y-V plasty. In women a very acute vesicourethral angle may be corrected by transvaginal relaxation of supporting tissues.

## SPHINCTER CHANGES LEADING TO DECREASED RESISTANCE

Here again the principle of balance applies. The structures and supports of the sphincteric urethra must not be injured. If this occurs, intraluminal tension and passive resistance falls, resulting in incontinence. Escape of urine only with sudden increase in intra-abdominal pressure as in coughing, sneezing, laughing or straining is called stress incontinence.

### Incontinence in the Male

Prostatic surgery of any type is the most common cause for incontinence in males. The important membranous urethra may be stretched, lacerated or incised and/or coagulated during a transurethral resection, or it may be damaged by infection. The striated muscle may be but is usually not damaged[9] and remains capable of voluntary movement but this ability is not an index of passive or unconscious continence.[9] Excluding those with chronic brain syndrome for obvious reasons, patients who show such voluntary contraction but remain incontinent are not to be judged as uncooperative or uninterested in achieving control.[11] The striated

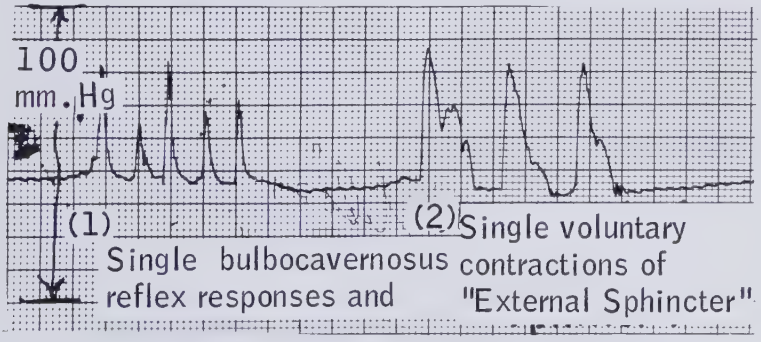


Figure 2. Two types of contraction at the striated portion of the sphincter ("external sphincter") recorded with dynamic sphincterometer[12] in a male, age 71, with chronic lymphatic leukemia, after transurethral resection. On left, bulbocavernosus reflex responses obtained by lightly pinching the glans penis, indicative of intact somatic sacral cord outflow. On right, voluntary contractions which are not evidence of passive continence.

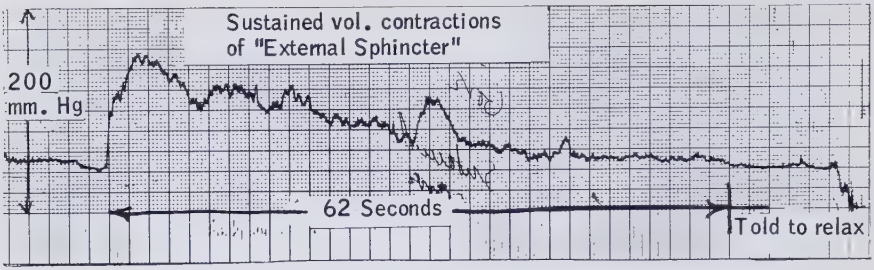


Figure 3. Fatigability of striated muscle of the sphincter recorded with the dynamic sphincterometer.[12] A male, age 68, with benign prostatic hypertrophy, commanded to "keep water shut off" with maximum effort. From an initial peak lasting about 2 seconds, the intensity of contraction gradually fell off to the resting level at 62 seconds, then the patient was allowed to relax. Some patients can sustain a low level of tension after the initial rise for several minutes (one patient up to eight) but with extreme effort and discomfort.

portion of the sphincter, apart from its role of providing some tension in passive continence through its postural tone, can pinch off the urethra at maximal force for only a few seconds.[11, 12] It can do so for one or more minutes with great discomfort and effort at a lower level of tension[12] in its attempt to hold back the constant dribble of total incontinence or the normal induced or imminent flow until the detrusor reverses its state of contraction to one of relaxation.

TREATMENT. Apparently injury to the membranous urethra is not always permanent. Incontinence may disappear spontaneously after a few days or weeks; in some cases of radical prostatectomy this may require many months. Mobilization of the structures of the perineal and pelvic floor muscles through active exercises or passive electrical stimulation may also be of benefit. To what extent improved striated muscle tonus is related is undetermined. Permanent incontinence when present is a formidable challenge[11, 15, 28] and the many theoretically reasonable methods of surgical correction include plication and narrowing of the urethra, slings of fascia or ribbon gut, muscle transplants, interposition of fat or paraffin about the apex of the prostate, and others. All have lacked practical consistency and the general results have been described as disenchanting.[28] The Berry operation[3] and its inevitable modifications which interpose an anchored prosthesis between the bulbocavernosus muscle and the bulbous urethra, compressing and kinking the latter against the diaphragm, is showing the most promise of dependability in cases with minimal incontinence. Cystourethropexy as for women has shown some benefit.[13, 27] Elongation of the urethra for severe incontinence using healthy bladder wall is undergoing trial.

## Incontinence in the Female

This may be congenital, menopausal or postoperative but the most common type of involuntary loss of urine in women is associated with child-

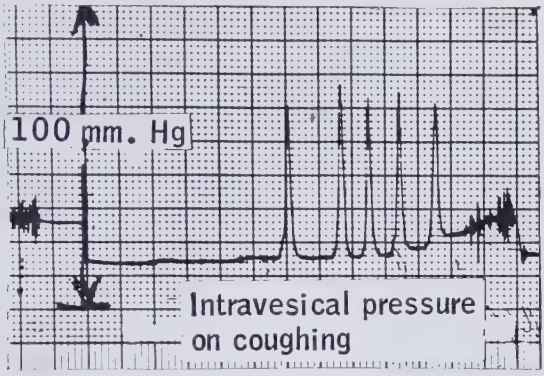


Figure 4. To illustrate how intra-abdominal pressure affects intravesical pressure rise with each cough. A male, age 34, with lower motor neuron bladder, with sphincterometer balloon cuff[12] in empty bladder.

birth trauma especially in multipara. The trauma pulls the contused and lacerated urethra away from the symphysis pubis. The pubococcygeus is stretched and relaxed, with the bladder neck becoming patulous and funneled, the urethra short and flaccid and poised low in the pelvis as in voiding, while the vesicourethral angle is a straight line.[13, 14] Any increase in intra-abdominal pressure causes stress incontinence, and both reflex or voluntary contraction of the striated musculature fails because of the poor supports. Lapides believes that an abnormally short urethra in the standing position is the basic predisposition to stress incontinence. In the menopause, loss of mucosal turgidity and elasticity and poor coaptation of the walls from deficiency of estrogenic hormone is considered important.

TREATMENT. Perineal and pelvic floor muscle exercises are said to account for benefit in many of these patients. The remainder require surgical correction, commonly the anterior vaginal wall approach, but also the Marshall-Marchetti-Krantz operation or its equivalent in which the urethra and the portion of bladder wall just proximal to the neck is tacked up to the tissues of the pubic bone. Depending upon the author, such cystourethropexies succeed in 80 to 100 per cent of the cases. The urethra is adequately elongated and made taut and narrow to increase its intraluminal tension and the vesicourethral angle is re-established.[24] For menopausal incontinence, estrogenic hormone is administered but cystourethropexy may also be required.

## THE SPHINCTER IN NEUROGENIC DISORDERS

As in mechanical disorders, there is a disturbance of balance between expulsive and resistive forces. Prostatic hypertrophy and fibrotic contracture complicate the problem.

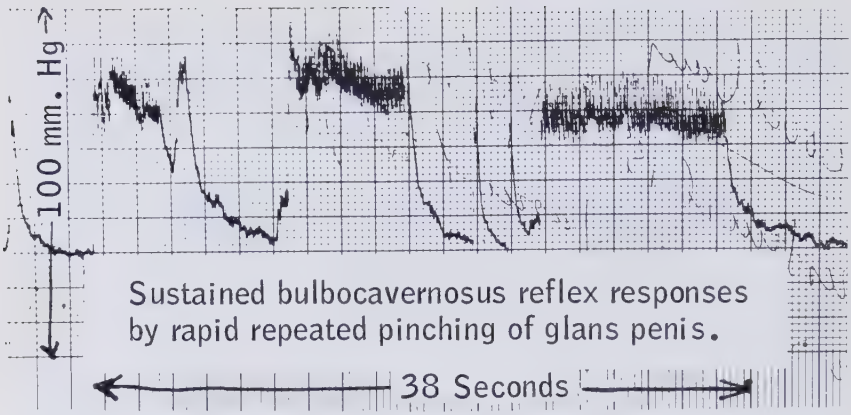


Figure 5. Dynamic sphincterometer[12] used to simulate spasm effect at the striated muscle portion of the sphincter with three prolonged bulbocavernosus reflex responses obtained in a male, age 71, after transurethral resection, by repeated rapid light pinching of the glans.

**Increase in Sphincteric Resistance**

This is typified by lesions above the sacral cord level. Both bladder structures and the striated musculature of the pelvic floor and perineum, including the striated portion of the sphincter as far up as the bladder neck, become hypertonic and respond reflexly in an exaggerated manner to afferent stimuli from within themselves or adjacent organs and structures. This complex of uninhibited and uncoordinated reflex responses has been brought to notice chiefly by Bors and his associates.[1, 7, 8] Calculi, infection, distention of the bladder or rectum, catheter manipulations and contractions of muscles all can set off intense striated muscle spasms, the net effect at the sphincteric urethra being intermittent[1, 5] or complete obstruction. A reciprocal reflex relationship[5, 7, 11] between the detrusor and the striated musculature of the perineum and pelvic floor contrive to shut off the stream as soon as it starts. When the bladder neck is drawn up by the striated muscle spasms, the bladder contractions cease.[1, 6] This is the picture of the reflex "upper motor neuron bladder" as characterized by Bors.

TREATMENT is directed to reducing the resistance produced by the hypertonic or spastic striated musculature. Conservative methods include mechanical weakening of the striated portion of the sphincter by endoscopic means, partial excision of or incision into bladder neck transvesically, and pudendal neurotomies or repeated instillations of 0.25 per cent tetracaine (Pontocaine) solution[7] into the bladder to alter the abnormal reflex patterns. More drastic measures include selective sacral neurotomies, excision of the sacral cord itself and intrathecal alcohol injections, the objective being a conversion of this type of bladder to one of a lower motor neuron type whose advantages will be discussed next.

### Decrease in Sphincteric Resistance

This results from lesions of the sacral cord and cauda equina. A "lower motor neuron bladder" is produced incapable of contracting reflexly, while the perineal and pelvic floor musculature undergoes flaccid paralysis. Spasms are absent and intraluminal tension of the urethra is decreased but not enough to allow escape of urine at rest. The bladder neck is wide, low in the pelvis, in the "ready" position for voiding such that voluntary abdominal effort when present, or Credé pressure serves to empty the bladder.

In both upper and lower motor types adjunct TREATMENT includes transurethral resection or open procedures at the vesical neck when muscular hypertrophy or contracture or prostatic enlargement appear as organic factors of resistance.

### The Sphincters in Neurogenic Disorders of Infants and Children

Complete and incomplete high and low cord lesions from birth trauma, lipomas, and mostly congenital defects of the spine and cord comprise this group and are comparable to those in adults except for the difficulties inherent in the care of small humans with growth potential and instability of the lesions, uncertainty of the neurosurgical corrective efforts, and wide range of symptoms. In high lesions the smooth muscle of the bladder, neck and urethra is hypertrophied and sphincter resistance high. In the low lesions at the conus or cauda equina, the sphincteric urethra is patulous and flaccid and associated with an atonic bladder. Chronic infection and fibrosis as in adults compound the therapeutic difficulties. There is some degree of incontinence or obstruction.

TREATMENT ranges from the conservative to surgical resistance-reducing procedures on the bladder neck and conversion to lower motor neurone bladder for high lesions as in adults.[2, 17] Some children attain acceptable continence by puberty but not later. Many die by the end of two years.[17] Those who reach school age, especially females, benefit from ileal loop conduit urinary diversion.

### Relative Increase in Sphincteric Resistance

When sensory pathways have been disrupted, typified by the tabetic bladder or pseudotabetic bladder of uncontrolled diabetes, there is loss of sensation, overdistention, atrophy and loss of detrusor contractility and expulsive force. The sphincteric urethra becomes relatively too resistant. Abdominal effort and scheduled voidings become necessary.

TREATMENT consists of a transurethral resection of the neck and hypertrophic prostatic tissue if present.

### The Sphincter in Idiopathic Hypotonic or Atonic Bladders

This entity is poorly defined. There are no obvious neurological

deficits. The bladder, however, resembles that of the sensory type in having little or no sensation, large capacity and no expulsive force. Here, again, sphincteric urethral intraluminal tension is relatively too high to be overcome.

TREATMENT in addition to a transurethral resection of the neck and prostate gland consists in excising a large portion of the bladder fundus to reduce the capacity. Total prostatectomy as for carcinoma of the prostate gland has been suggested as a further means of reducing drastically the sphincteric resistance.

## SUMMARY

The urinary sphincter system consists of a tubular extension of the bladder containing elastic tissue with a striated muscle collar chiefly where it traverses the urogenital diaphragm. It is the entire female urethra and the prostatic and membranous urethra of the male. There is no internal sphincter structure. "Unconscious continence" is the result of tension produced by the smooth muscle, elastic tissue and the tonus of the surrounding striated musculature further aided by the supporting structures which maintain the urethra taut and elongated.

Destruction of either end of the sphincteric tube does not result in incontinence. If both ends are damaged, as by misadventure in prostate surgery, incontinence appears. Stress incontinence in some degree results with sudden increase in intra-abdominal pressure if the supporting structures are damaged or the striated musculature is damaged or paralyzed. Normally a brisk reflex contraction of the striated musculature prevents this. Coughing, sneezing, lifting, etc., cause such increases in pressure. The striated musculature expedites interruption of micturition but is incapable of sustained contraction indefinitely and ability to contract the striated portion of the sphincter voluntarily is not evidence of unconscious continence. The smooth muscle of the bladder neck and the trigone and the striated musculature of the sphincter and perineum play a role in ejaculation.

Physical impediments and striated muscle spasms cause increased sphincteric resistance and obstruction. The basic dysfunction is the inability of the detrusor to open wide the bladder neck and shorten the urethra, prerequisites for normal voiding. Relative increase in sphincteric resistance exists when the detrusor is hypotonic or atonic. Treatment attempts to reduce the resistance.

Decrease in sphincteric resistance occurs in the wake of simultaneous damage to both ends of the sphincteric urethra and when supporting structures are relaxed or the striated musculature is paralyzed. The urethra becomes flaccid and lies low in the pelvis with a patulous neck and poor coaptation of its walls. Correction of prostate surgery incontinence, in

which the membranous urethra is damaged in addition to the neck, is difficult to achieve consistently. Stress incontinence in women is much more amenable to both conservative and surgical treatment.

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# Postprostatectomy Urinary Incontinence and Some Experiences with the Berry Procedure

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## ETIOLOGY OF URINARY INCONTINENCE

Urinary incontinence or enuresis is the involuntary discharge of urine, irrespective of the etiology.

Nocturnal enuresis occurs mostly in young children, but may persist throughout life or may cease at any time after age three. Not all, but the majority of adults with nocturnal enuresis usually have a pathological condition to account for the incontinence. I am referring now to those adults other than the psychopathic or psychogenic holdovers from childhood: this reference alludes to those with myelomeningocele, exstrophy of the bladder, epispadias, and central nervous system disease such as birth injury or hydrocephalus. Diurnal enuresis occurs in children and adults with epispadias and exstrophy as well as neuromuscular and neurogenic disease.

Another cause of urinary incontinence in any age group in both sexes is pelvic injury including fracture and trauma which can result from manifold situations such as fragmentation shell bursts, blast injury and gunshot wounds. Let us not overlook the ever present skiing and automobile accidents. Not all such pelvic injuries are fortuitous; some are iatrogenic and follow instrumentation. Some cases of enuresis or incontinence may be the result of congenital or acquired diverticula of the bladder and anterior (occasionally the posterior) urethra.

In some of the neurogenic types of incontinence, dribbling may be the first symptom or tip-off to central nervous system disease, as is so frequently the case in the parkinsonian syndrome, multiple sclerosis

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and tertiary syphilis. Senility must be considered in the etiology, as well as paradoxical overflow which may be secondary to obstruction caused by benign hyperplasia or malignant hypertrophy of the prostate gland. Stone and pedunculated adenoma may cause incontinence by acting as a ball valve. Either acute or chronic cystitis may be the offender. Anomalies such as ectopic ureteral orifices, abnormal urethral configuration with congenital stenosis and stricture should not be passed over lightly.

## MECHANISMS OF URINARY CONTINENCE

Frankly, I am not certain why humans or animals are continent of urine and feces, and I am not convinced that anyone really knows. Stewart, Belt and Belt, Goodwin and Letourneau[20] state, "The mechanism of continence is not completely understood." Perhaps we should manifest more interest in research along these lines in an attempt to establish the mechanism of continence in man. If this could be accomplished we might better understand the problem of urinary incontinence. Again, if we could exactly define the complicated act of micturition, possibly we could approach the problem of postprostatectomy urinary incontinence with a more vivid perspective.

For all practical purposes my first query of why we are continent of urine was answered in an article by Elliot[6] back in 1954. In this article he showed that the urethra is invested with circular and longitudinal coats of smooth muscle from the bladder neck to the anterior aspect of the triangular ligament. Interspersed throughout this smooth muscle and connective tissue are fibers of striated muscle, sparse in the vicinity of the vesical neck but becoming more numerous and better developed as they further and further encompass the urethra until at a point within the urogenital diaphragm they completely surround the urethra and form the compressor urethrae. Rolnick[19] mentions that Young and Wesson[26] described the external sphincter as "beginning at the mesiolateral aspect of the vesical orifice." Here the sphincter fibers are few and do not encircle the urethra, but they pass downward and backward, increasing in number and extending more posteriorly in a circular manner. At a point opposite the apex of the prostate they are joined in a raphe, forming a circular sheath around the urethra.

In more recent times Lapides[10, 11] had done a tremendous amount of research in an effort to determine the structure and functions of the internal vesical sphincter and the role of striated muscle in urination. McCrea[15] states that both the internal sphincter and the external urethral sphincter are composed of both smooth and striated muscle and from his description one would assume he meant the muscle fibers of the neck descended through the prostatic urethra to join with those muscle fibers of both types ascending from the pendulous and proximal or membranous urethra. According to

Kost,[9] only within the last year has any mention been made of striated muscle being a normal component of the prostate gland and its capsule. This statement is not quite exact—Beneventi and Marshall[1] described this very well in 1956 and so did Wallace[24] in 1904.

Lapides[11] has done monumental work in demonstrating that, in the dog at least, continence may be maintained in the absence of either the internal or external sphincter but not both. The development of his bladder tube in dogs with resultant continence was very ingenious and bears out Berry's[2, 3] contention in at least two articles that urethral resistance is paramount to good urinary continence.

Ernest F. Hock[8] emphasizes again and again that continence is not achieved by active sphincteric contraction, but by the resistance of the urethra to intravesical pressure. Beneventi and Marshall[1] state as a prelude to an article entitled "Some Studies of Urinary Incontinence in Man"[1] that "the urinary sphincters and their actions are so poorly understood that ideal correction of postprostatectomy incontinence is not often achieved." In examination of many slides from the full length of the prostatic urethra they did not find a clearly defined circumferential band of either smooth or striated muscle at the vesical outlet. In short, the external striated sphincter was thick and extensive, not a thin, iris-like structure. "If it were a thin iris-like structure, damage of any significance would seem likely to be a complete division with severe disturbances and small hope of spontaneous improvement."

It becomes apparent that despite extensive research by many honest and able observers we are still in the dark as to why humans are continent of urine.

## THE PHYSIOLOGY OF MICTURITION

There has been since the time of Galen and there continues to be two schools of thought on whether smooth muscle alone can initiate and terminate micturition by direct cortical control. Those who are opposed to this hypothesis believe that striated or voluntary muscle activity is essential to initiation, continuation and termination of urination. Muellner[17] is of the opinion that man utilizes a group of striated, somatically innervated skeletal muscles to control urination, and he calls this group of muscles the "voluntary mechanism." The complex consists of the thoracic diaphragm, the muscles of the abdominal wall and the levator ani with its two component parts, the pubococcygeus and the ileococcygeus. He writes, "Deliberate micturition at any degree of bladder filling begins with a moderate increase in intra-abdominal pressure which is directed toward the bladder neck. The increase in intra-abdominal pressure at the beginning of micturition, caused by the action of the thoracic diaphragm and of the abdominal musculature, is associated with a relaxation of the pubococcyg-

eus and ileococcygeus 'pelvic floor.' " This, according to Muellner,[17] causes the bladder neck to be pushed downward in the pelvis and it is this downward tug on the bladder neck that acts as the stimulus for the contraction of the detrusor, which by the way is smooth muscle, therefore involuntary. He further claims that the bladder neck thus becomes the "trigger area" and it is at this point that the voluntary mechanism and the involuntary detrusor are joined. The impulses for the contraction of the detrusor spread from the bladder neck to the base, to the sides, to the dome. In order to interrupt the urinary stream or, in other words, to stop voiding voluntarily, the reverse process to voluntary voiding must take place: namely, the contraction of the complete levator ani group. This allows the bladder neck to rise, causing the internal sphincter to close abruptly.

Ernest F. Hock[8] has, I believe, a good common sense explanation of urinary incontinence when he says, "For a thorough understanding of urinary incontinence a brief discussion of the physiology of micturition will be helpful." He goes on to say that "We have accepted that urination is initiated by a contraction of the detrusor which reflexly relaxes the urethral sphincters. Although this is true under experimental conditions it cannot explain how urination can be voluntarily started when the bladder contains only a small amount of urine, since neither the detrusor nor the internal sphincter is subject to voluntary influence. . . . Hence one must conclude that in the inactive stage, the urethra offers a resistance which normally cannot be overcome by an increase in the intravesical pressure. Before the bladder can empty, the urethral resistance must be decreased and this decrease is under voluntary control. Permanent loss of resistance will produce incontinence and, conversely, permanent inability to diminish this resistance will produce urinary retention." Hock[8] goes on to say that "Since the anterior urethral wall is fixed, lowering of the bladder base separates the posterior from the anterior wall, resulting in a decrease of the urethral resistance. Closure of the urethra is achieved by the return of normal tonus to the pelvic floor muscles or by their contraction, especially the pubococcygeal muscles. This mechanism indicates that at least part of the urethral resistance is due to anterior-posterior compression between the pelvic bones and the pelvic floor rather than a circular contraction of the sphincters." I will have more to say about this later.

I believe that micturition is accomplished by a two-fold mechanism, nervous and muscular. In childhood the act is purely reflex and at first uncontrolled, but as time goes on the normal child will develop inhibitory control centers which allow the bladder to accommodate and increase its capacity before the stretch reflex signals evacuation time, and at this point voluntary control takes over until a proper voiding situation is found. From observation and cinefluorography I have noted that urine in the bladder is held at the vesical neck before prostatectomy of any type and that following removal of the prostate gland, regardless of the route, the urine column is held at the apex of the prostate in those patients who are continent post-

operatively and the bladder will be in some stage of distention. Now in that unfortunate group of patients who are incontinent following any type of prostatectomy, the urine column extends into the proximal urethra and continues into the pendulous portion and out the meatus and the bladder will be collapsed.

My personal concept of urinary continence is this: The proximal urethra, which includes the vesical neck, the prostatic and membranous portions, is composed of transitional type mucosa, surrounded by a layer of elastic tissue. Interspersed through this layer of elastic tissue are fibers of both smooth and striated muscle or, if you please, involuntary and voluntary muscle. These anatomical components then give structure, tone and resilience to the urethra. Surrounding this portion of the urethra except within the urogenital diaphragm is the prostate gland, be it capsule in the child or capsule plus adenomatous hyperplasia or malignant hypertrophy in the adult or aged. The urethral walls approximate each other, the mucosa forms rugae, thus the whole complex with normal or proper tonus provides an involuntary water-tight tube, with sufficient resistance in the normal state to insure continence.

## POSTPROSTECTOMY URINARY INCONTINENCE

Up to this point I have attempted to show how the bladder retains urine until it is triggered to the point of evacuation and finally how continence can be maintained without voluntary control. Urinary incontinence is not a common sequela of any of the different types of prostatectomy. Neither is it unusual, and when it occurs it constitutes a sad problem. Since 1949 or therabouts there has been an increased interest in the cause and treatment of this condition. Certainly from the number of papers since 1961 one might assume that either there are more cases of incontinence or that more cases are recognized and in an attempt to cure them by several different methods these cases are reported; how many unreported cases exist is unknown.

This is the proper place to ask an unanswered question: Why are some patients incontinent following any type of prostatectomy? Rolnick and Arnheim[19] state that incontinence is more apt to follow perineal prostatectomy, not because of injury to the sphincter but "(1) because the nerve fibers innervating the external sphincter come in from the posterior aspect and the operative approach through this area may result in nerve injury, (2) the perineal muscles play some part in the act of micturition and urinary control and may be damaged in the perineal approach to the prostate."

Edwin Davis[5] gives credence to the atrophy of disuse theory as an explanation of postprostatectomy urinary incontinence. Elliot[6] states, "The conclusion seems inescapable that postoperative incontinence is due to the excessive removal of smooth muscle and connective tissue in the

vicinity of the prostatic apex and membranous urethra." H. H. Young[27] ascribed the frequency of urinary incontinence following radical perineal prostatectomy to injury of the external sphincter or its nerve supply. Hock[8] maintains that if the urethral resistance is diminished below a certain point, incontinence will result, its severity depending upon the degree of decrease of urethral resistance. Lapides[11] writes: "Theoretically, stress incontinence can occur whenever the intraluminal resistance of the urethra is decreased below a certain value. The decrease in resistance may be due to a decrease in the tension exerted by the urethral wall upon its lumen, a decrease in urethral length or an increase in the inside diameter of the tube." Berry[2] suggests that urinary incontinence following prostatectomy appears to be related to a disturbance in the neuromuscular mechanism causing various degrees of disparity between resistance of the external sphincter and the expulsive force of the detrusor.

**Corrective Procedures**

Now then, whatever the cause, we have a leaking, malodorus, unhappy patient, and the question arises: What shall we do? I believe it expedient to review some of the recent attempts to correct urinary incontinence. To begin, H. H. Young,[28] in 1908, achieved urinary continence by narrowing the lumen of the urethra and bladder neck to a very small caliber. However, these repairs caused stricture and were a source of constant attention. Next came the Lowsley-Hunt[13] plication method, the results of which were unsatisfactory after a short space of time. This was followed by the Verges Flaque[22] method of splitting the external rectal sphincter and enveloping the urethra just beyond the bulb with the internal one-half of the rectal sphincter, which was sutured to its original site. The Marshall-Marchetti-Krantz[14] procedure for stress incontinence in women has been used in males and is a wonderful step in the right direction. Quakels[18] injects paraffin into the perineum. Vincent[23] maintains that urinary continence may be restored by upward perineal pressure from a polyvinyl chloride saddle suspended by adjustable straps from a wide belt. Penetrating and resting upon this saddle is an inflatable balloon, with a tube running to the individual's pocket so that he may inflate or deflate at will. He reports very favorable results in men, women and children. I have personally seen some of his cases and they were remarkable. In the enuretic and stress incontinence group, some patients were able to discontinue use of the appliances after a short course of perineal exercises and electrical stimulation, although such measures were ineffective before the appliance was used. The application of the appliances is shown in Figure 1.

Girgis[7] has a procedure for reinforcing the external urethral sphincter with an absorbable collagen prosthesis which imbricates the bulbocavernosus and levator ani muscles (see Figure 2). Guy Leadbetter, Jr.[12] devised a surgical technique for curing incontinence by lengthening the urethra with a muscular tube and reimplanting the ureters more superiorly.

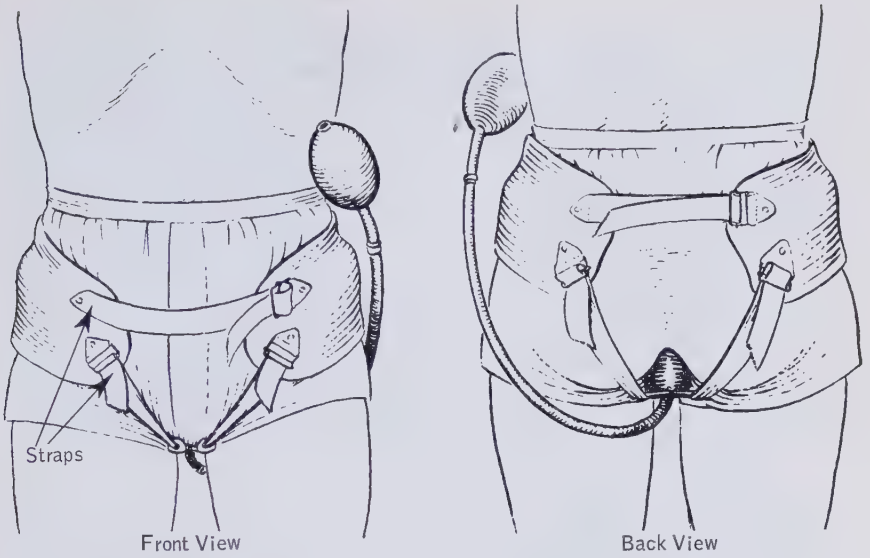


Figure 1. Vincent's method of treating urinary incontinence by upward perineal pressure from a polyvinyl chloride saddle suspended by adjustable straps from a wide belt. *Front View.* A hip shield is molded to fit over hip bone. All the front straps may be slackened slightly after the back straps have been fully tightened. *Back View.* In this picture the lower straps are slackened off in order to show the balloon in position, but they should be tightened as much as possible when the balloon is worn. (Courtesy of S. A. Vincent, F.R.C.S., Belfast, Ireland.)

More recently, Dr. Kenneth P. Caldwell[4] of England has used electromyography for continuous unfatigued contractions of the rectal and urethral sphincters. Watkins, Straffon, and Poutasse[25] modified the Berry[2] procedure by using medical silastic (silicone rubber) to replace the Berry[2] acrylic prosthesis. Instead of wire sutures, they use strips of dacron-impregnated silastic for anchoring the prosthesis. Their results in five patients were encouraging. (See Figs. 3 and 4.)

Milner[16] employs a strip of bladder which surrounds the urethra at the vesicourethral junction to control stress incontinence in women and reports a high percentage of cures. Uhle, Bradley and MacKinney[21] describe an operation in which suprapubic vesicourethral suspension was used for stress incontinence in women with an 85 per cent cure. Edwin Davis[5] believes that sphincter "exercise" treatment, personally supervised and systematically carried out, tends to shorten materially the period of incapacity. Verges Flaque[22] concludes that "certain cases of incontinence of urine following prostatectomy are curable if treated by properly performed exercises to develop the contractile ability of the external sphincter."

## The Berry Procedure

What else can be done to control urinary incontinence? If my assumption that the internal vesical sphincter, the smooth and voluntary muscle

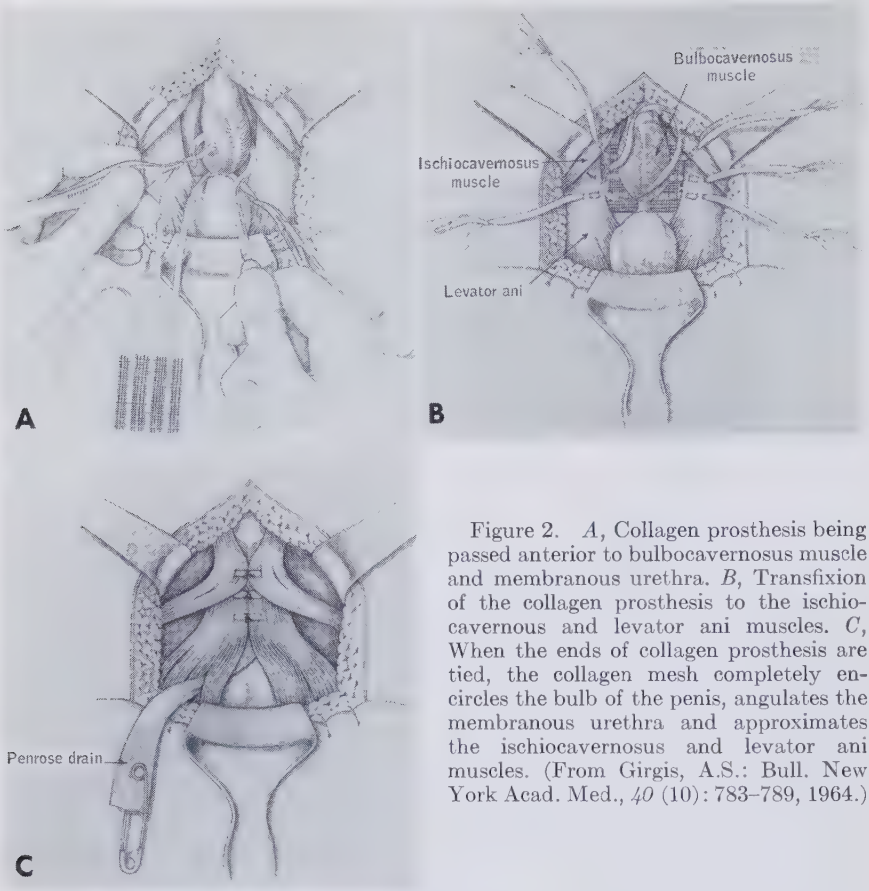


Figure 2. *A*, Collagen prosthesis being passed anterior to bulbocavernosus muscle and membranous urethra. *B*, Transfixion of the collagen prosthesis to the ischiocavernous and levator ani muscles. *C*, When the ends of collagen prosthesis are tied, the collagen mesh completely encircles the bulb of the penis, angulates the membranous urethra and approximates the ischiocavernosus and levator ani muscles. (From Girgis, A.S.: Bull. New York Acad. Med., *40* (10): 783–789, 1964.)

within the elastic walls of the urethra, and the external sphincter, which is partly smooth muscle, cause sufficient resistance to vesical pressure to insure continence is correct, then anything that upsets this equilibrium may cause incontinence. Following prostatectomy by any route, this equilibrium is upset. Now whether incontinence is the result of iatrogenic trauma, local ischemia, the atrophy of disuse or a deficit of tissue matters little to the leaking patient. Actually, it matters little to the urologist, apart from his interest in it academically. What is of primary importance is how we can re-establish continence in these patients. For me, the most logical approach is to attempt to restore the original anatomical relationship of the structures involved. Exercises will not cure incontinence. My concept is to restore proximity of the walls of the urethra by compression, to lengthen the urethra, if possible, by external pressure, and finally, to increase urethral resistance by kinking the urethra. This can be done in some cases by implantation of an acrylic prosthesis between the bulbocavernosus muscle and the bulbous urethra. The procedure was first performed by the writer in 1958, and in 1961 a description of the operation

and the results in 11 cases were reported. The results although poor in 55 per cent were considered good in 45 per cent after 22 months observation in some cases. Since that time other urologists, namely Abeshouse, Belt, Leadbetter, Milner, Poutasse and Uhle, have used the procedure and all have obtained good results in approximately 50 per cent of their cases. Since the original paper there have been several changes, some in the technique and several in the prosthesis. Originally the procedure was utilized in all types of urinary incontinence; however, at present I believe that its only indication is postprostatectomy urinary incontinence.

Prior to operation cystourethrography, cystometrography, cystourethroscopy and investigations of the upper urinary tract are carried out following a complete physical examination. These studies are rewarding as they may reveal vesical or urethral diverticula, calculi in the bladder, prostatic fossa and urethra and urethral stricture. Unexcised hypertrophic

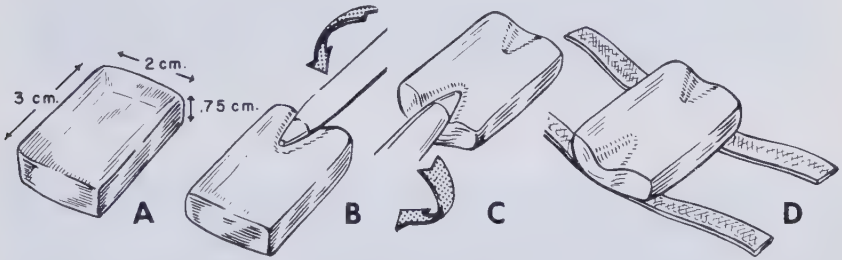


Figure 3. Sketch showing the fashioning of the medical silastic prosthesis. *A*, A raw block of medical silastic of the approximate dimensions of the implant. *B*, Fashioning a urethral groove in the implant with a cylindric instrument. *C*, Rounding off the corners of the implant with the same cylindric instrument. *D*, Placement of the silastic block on anchoring strips of dacron-impregnated silastic—the completed medical silastic implant. (From Watkins, J. K., Straffon, R. A. and Poutasse, M.D.: Cleveland Clinic Quart. *31:* 157–162, 1964.)

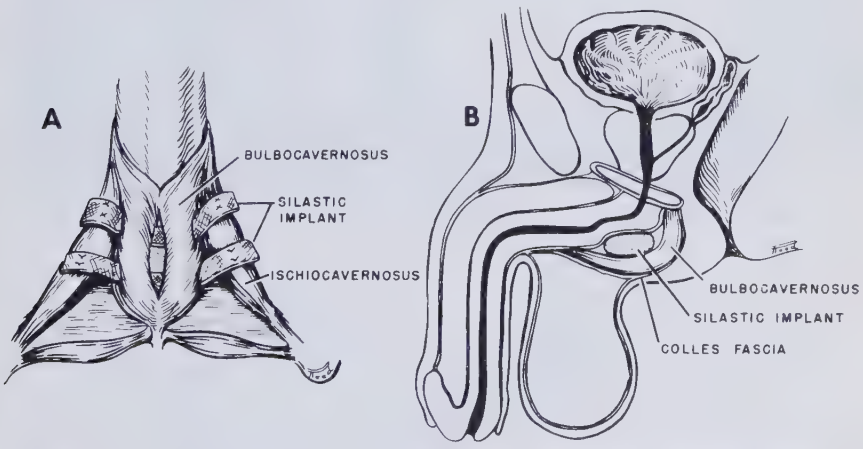


Figure 4. Sketch showing the medical silastic prosthesis implanted in position for control of urinary incontinence in the male. *A*, Perineal view. *B*, Sagittal view.

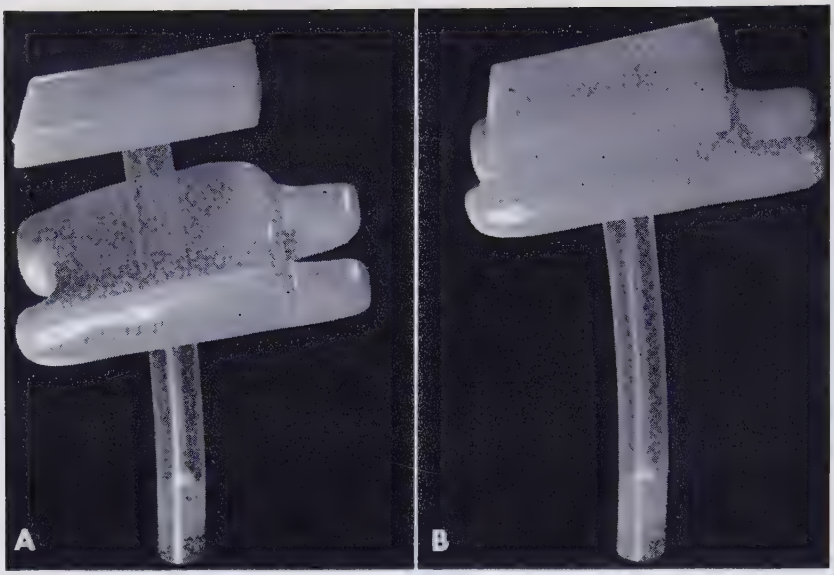


Figure 5. *A*, The new acrylic prosthesis through which passes the stem of the silastic balloon. *B*, The silastic balloon pulled into place.

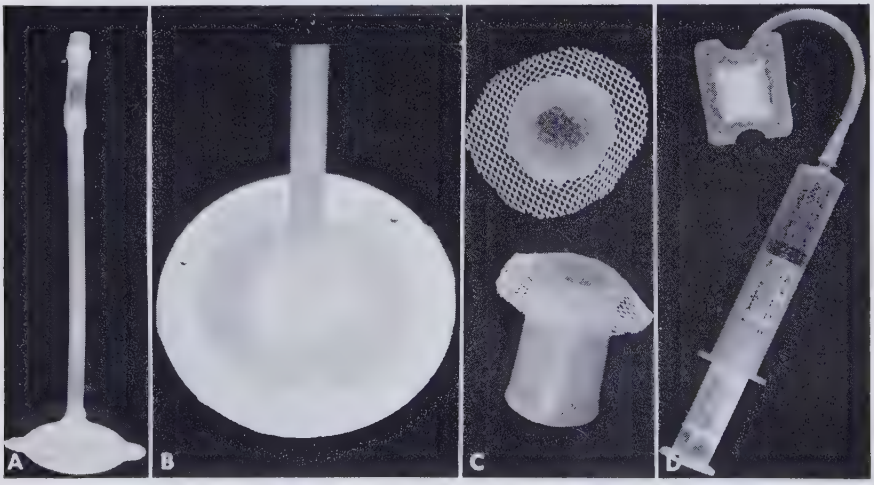


Figure 6. *A*, *B*, Another type of silastic balloon. *C*, Valve type of sleeve prosthesis to be used in vesical neck. *D*, Silastic balloon injected with silastic liquid which has solidified.

tissue, especially the anterior commissure, may be causing obstruction with overflow. Stricture of the urethra is not uncommon following any type of prostatectomy. Neurogenic disease of either flaccid or spastic type will give incontinence.

Figure 5 shows the new acrylic prosthesis and the silastic balloon. Figure 6 shows other types of prostheses that I am experimenting with.

An attempt is made to sterilize the bowel for 24 to 36 hours prior to operation using either neomycin or succinylsulfathiazole (Sulfasuxidine). The perineum and suprapubic areas up to the umbilicus are shaved three days before operation and this area is scrubbed with pHisohex daily until the operation. *Note*: Be sure to rinse the pHisohex off the skin and genitalia especially or you may produce a severe dermatitis. Since this routine was adopted postoperative infections have practically disappeared.

THE OPERATION. The original technique is illustrated in Figure 7. The step-by-step description to follow is of the operation as it is done today. The patient is anesthetized by spinal technique and placed in a relaxed lithotomy position. The perineum and suprapubic areas are scrubbed with hexachlorophene (pHisohex) and aqueous benzalkonium (Zephiran) solution and the appropriate drapes are applied. Sew a towel across the perineum just above the anal verge. Introduce the Lowsley anterior tractor. A vertical incision is made in the perineum from a point just below the scrotoperineal junction to a point about 2 cm. above the anal margin. This incision is deepened through the skin, subcutaneous tissue, the superficial and deep layers of Colles' fascia down to Buck's fascia which covers the bulb. Buck's fascia is incised in the midline over the entire length of the bulbocavernosus muscle, and by sharp and blunt dissection this muscle can be exposed in its entirety. The ischiocavernos

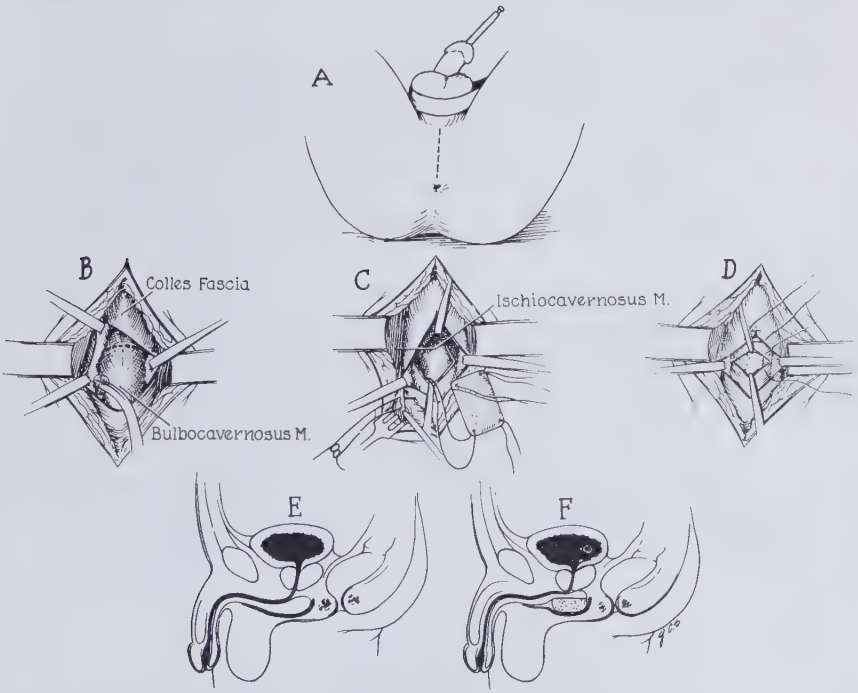


Figure 7. Implantation of Berry prosthesis. This is the original Berry procedure showing different steps (*A*, *B*, *C*, *D*). The principle of the operation is depicted in *E* and *F*. (From J. Urology, May, 1961.)

muscles which lie just lateral to the bulb are exposed at their origins only along the inferior surfaces of the ascending rami. This is the first marked change in the technique; instead of splitting the muscle in line with the fibers and developing a pocket, I now simply place the prosthesis directly on the bulbocavernosus muscle.

A choice is made of prosthesis using the largest that will fit beneath the angle of the symphysis pubis. Pass a 10-inch strand wire through each of the distal ports and tie in the middle. Thread both strands of wire through the eye of a small, strong, full-curve Mayo needle. Pass the threaded needle through the bone of the symphysis pubis from inside out. If you so desire you can make two passes through the bone of the symphysis with a single strand of wire. Whichever way you decide, all four corners should be placed; the two posterior guide wires are passed through the ascending ramus of the ischium. Now, on the two distal wires or those through the symphysis, if you elect to pass them together, then you must unload one wire from the needle's eye and take a longitudinal bite of the fascia covering the ischiocavernosus muscle. Do the same with the other anterior port.

Now remove the Lowsley tractor. Place the two posterior guide wires. Here is the second and probably the most important change. At present I believe the Berry silastic balloon will improve the chances of a cure in a large number of cases. Therefore, pass the tube of the balloon through the fenestration in the center of the acrylic prosthesis and seat the deflated balloon. Now press the prostheses (both of them) firmly against the bulbocavernosus muscle and snug up the wires on all four corners and tie the wires. You need have no fear of getting the prosthesis too tight. I have not had a fistula or complete obstruction in a single case. Close Buck's fascia over the prosthesis, leaving the tube protruding through the closure of one layer of Colles' fascia.

Now bend the tube into the scrotum and bury it with two black silk No. 0 sutures. This is very important because the tube has a tendency to erode through the perineal closure. It has happened three times in 26 cases. Take two more rows of sutures with chromic No. 0 catgut to close the integuments of the perineum. The skin may be closed with wire, black silk or a subcuticular stitch. There has been no indication to drain this incision, which has been irrigated with 1 per cent neomycin solution before closure. An indwelling catheter should not be used as it may and has caused erosion and fistulous formation which necessitate removal of the prosthesis. Apply a pressure dressing for the first 12 hours. I believe it obviates hematoma formation.

## SUMMARY AND CONCLUSION

I have reviewed the literature since 1941 and have tried to present the views of some of the finest minds and best researchers in the field of urology both at home and abroad. In the final analysis no one is sure why we are

continent. No one is sure how we micturate and finally no one knows why we have incontinent patients both preoperatively and postoperatively. I have presented the views of several men on why we are continent and described their various methods of correcting postoperative urinary incontinence, concluding with a complete description of the Berry prodecure, especially the new prosthesis and the modified technique of implantation. It remains now only to mention results. Since 1958, I have performed 75 operations with the old procedure with good results in 45 per cent. I have now implanted 26 Berry silastic balloons since December, 1964. The results are much better thus far but the time is short and the results may be different in two years. Among these 26 cases the results are excellent in 22. I have distended only four of the balloons with sodium acetrizoate (Thixokon) and reburied the balloon tube; three of these patients are continent at present. One still dribbles.

In summary: 1. I am more than ever convinced that preoperative preparation of the bowel is of inestimable value.

2. Both the acrylic and the silastic prostheses are well tolerated by the body and the combination thus far has given a higher percentage of good results.

3. It appears that No. 2 multi-strand wire placed through the bones of the symphysis and ascending ramus of the ischium makes firmer pressure on the urethra.

4. The balloon seems to give better initial results. In case of failure simply distend the balloon with sodium acetrizoate. This is accomplished by making a nick in the perineum, picking up the tube, injecting 3 to 7 cc. of sodium acetrizoate, and reimplanting the tube again using heavy black silk sutures. This maneuver may lead to complications.

5. To date there have been no serious complications and no mortality.

6. The only complications I have had with the silastic balloon were due to injection of liquid silastic into the balloon, which disintegrated the valve of the balloon within 24 hours and necessitated its removal.

7. Sodium acetrizoate thus far has remained in the balloon, that is, it has not filtered through the walls, and beautiful cinefluorographic studies can be obtained if desired.

Although we do not know the exact cause of postoperative urinary incontinence, I suspect it is the destruction of the rosette effect of the urethral mucosa. This could explain why we are not completely successful in our treatment. However, with the stimulus and momentum of research I postulate that in the near future we will find the perfect substitute for the urethral sphincter and then we will no longer have with us the dribbler.

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# Urinary Diversion in Treatment of Carcinoma of Bladder

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## BACKGROUND

The treatment of carcinoma of the bladder has been a vexing challenge to medical men for centuries. The Egyptians over 5000 years ago, Hippocrates in a number of his aphorisms, and Galen reported conditions that suggested they could have been treating tumors of the bladder.[2] Surgery on the bladder was first performed in the sixteenth century and the French School of medicine was particularly active in its development.[32] Tumors have been destroyed by heat from a cautery, or even injection of boiling water, by electrical coagulation, external or internal radiation, or by locally applied chemical agents.[2] It can be truthfully stated that there is no method in vogue today for treatment of cancer of the bladder that has not been tried in some way or other since the days of antiquity.

Progress in the handling of this entity will require more knowledge of etiology and histopathology than is available today. There is still a vast area of uncertainty which offers a great challenge to investigators. We have well documented evidence that the metabolism of certain chemical elements is associated with the production of bladder cancer. If one could establish stages in the development of this disease, would local therapy alone be indicated in the early stages, or is this the time when complete eradication should be attempted by more radical procedures? Should the treatment of the earlier stages be surgical, chemical or radiation? Which technique should be reserved for treatment of recurrences or failures of early treatment? If surgery is to be the method of choice, should it be transurethral resection, segmental cystectomy or total cystectomy? Knowledge concerning lymphatic and vascular spread of tumor within the bladder wall suggests that radical extirpation of the malignant lesion is in the end a

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more logical approach to the problem than reserving extensive operative procedures for recurrent conditions or failure of other therapy. Early radical surgery may well apply to tumors that have extended into the muscular layer of the bladder, but is never indicated in the treatment of disease confined to the mucosal or submucosal layers. At the present time choice of treatment is dictated by all the pretherapy information we can accumulate on the individual patient. Total cystectomy, always including the prostate as part of the specimen, necessitates some form of urinary diversion.

Urinary diversion can be classified as either external or internal. The external diversion can be achieved by producing direct fistulas from the kidneys to the skin by means of a tube or by anastomosing the ureters to the skin. These methods employ some form of nephrostomy or cutaneous ureterostomy. The internal diversion requires anastomosis of the ureters either to the intact intestine as seen in ureterosigmoidostomy or ureterorectosigmoidostomy, or to an isolated loop of ileum whose distal end is brought out as an ileostomy or is directly anastomosed to the proximal urethra following total cystectomy. In external diversion there may be a constant discharge of excretions, which in the absence of leak-proof, odor-proof appliances, has made many patients feel socially unacceptable. Extensive research in the production of internal diversion has improved this situation, and patients tend to accept this state more readily than ever before.

Until the first total cystectomy was performed, which supposedly occurred in 1887 as performed by Bardenheuer,[32] the necessity for urinary diversion was never considered. Pawlick[32] in 1888 performed a total cystectomy successfully and diverted the urine by implanting the ureters into the vagina. Regardless of the route or the procedure, certain requirements must be fulfilled: (1) the method must be technically uncomplicated, (2) it must preserve renal function, and (3) it must provide good urinary excretion. For many years cystectomy itself was considered a very serious major procedure because of the poor results and consequences of urinary diversion. With more adequate preparation, preoperative and postoperative care, improvement in anesthesia, supportive measures and operative technique, we manage the problem of total cystectomy and urinary diversion much more frequently and with greater ease.

## EXTERNAL URINARY DIVERSION

### Nephrostomy

Early in the twentieth century Dr. Francis S. Watson,[2] a renowned surgeon and pioneer Boston urologist, published a review of his experiences in the treatment of bladder tumors. The universally poor results of all surgeons dealing with carcinoma of the bladder prompted him to advocate

total cystectomy as the procedure of choice. He reported such an operation preceded by bilateral nephrostomies in 1905. He had performed nephrostomies for a number of renal conditions, and had even designed a drainage apparatus for his patients to wear which was both successful and comfortable. Nephrostomy for diversion in bladder carcinoma was not readily adopted. It is often performed as an emergency, life-saving procedure. Frequently the temporary nephrostomy becomes a permanent feature because of the failure of renal function to return sufficiently to warrant more definitive procedures. Today one seldom, if ever, has to resort to temporary nephrostomy in the treatment of bladder tumors by cystectomy.

Performance of a nephrostomy is in most instances easily accomplished. Essentially it concerns producing a fistula from the renal pelvis through the renal cortex, with or without pyelotomy. Usually the pelvis can be exposed to direct vision but, should this not be the case, one can proceed with caution and accomplish what is frequently referred to as a "blind nephrostomy" by starting the fistula from the outer curvature of the kidney, through the cortex, to the pelvis. The earliest use of the term was by Albarran[1] in 1896, who actually performed a nephrostomy by incising the renal parenchyma and placing a tube in the pelvis. Since that time any number of procedures, using instruments such as probes, specula, cannulae, hooks and forceps, have been devised.

Papin[42] devised a method that is much in vogue today. After making a small opening in the pelvis or upper ureter, he placed a curved clamp in the lower calyx of the kidney and passed it through the parenchyma. He then pulled a tube back into the pelvis by means of the clamp. The use of an ordinary curved clamp or a renal pedicle clamp for pulling the well-known balloon type catheter into place makes for a rapid, readily accomplished nephrostomy with minimum morbidity. One must keep in mind the vascular patterns within the kidney to minimize hemorrhage. In closing the wound, the path of the emerging catheter must be planned to allow easy replacement later. Where permanent nephrostomy drainage is being planned, ligation of the upper ureter should be accomplished. When changing nephrostomy drains the tube is clamped at the skin surface before removing it so that one has a gauge as to the depth required for reinsertion of the replacement.

A balloon type of catheter may not be the best to use since the bag, when inflated, may interfere with the drainage of the catheter. There have been various apparatuses recommended for use with nephrostomy tubes, and even special types of nephrostomy tubes. There are a number of appliances one can wear to collect the urine and in many respects they must be adapted to the individual's anatomy. Straight catheters used on a rubber cuff at the skin's surface somewhat like that of the Brewer thoracotomy drain are available and in many instances are the best type of drainage tube to use. Certain precepts must be remembered if a nephrostomy is to be used: (1) the tube should be placed as low in the kidney as feasible, (2) it

should be brought out to the skin as straight as possible, (3) the shortest fistulous tract that can be achieved is desirable, and (4) the stoma should be as far anterior as possible to facilitate the use of drainage apparatus.

**Cutaneous Ureterostomy**

Actually, the earliest attempts at ureteral surgery were procedures necessitated by accidental severing of the ureter. Uniting the severed ends directly was considered the best treatment, and by 1900 this had been accomplished a number of times. Where this was not possible, attempts to achieve anastomosis to the bladder, urethra, rectum, colon and skin were made. After the first successful nephrectomy by Simon[32] in 1869, patients who had a ureter severed frequently had the involved kidney removed. In 1887 Edmunds and Ballance[19] reported the results of their experiments in ureterocutaneous anastomoses based on cadaver work. In 1891 Pozzi[40] performed a skin implantation following a retroperitoneal procedure in a patient who subsequently underwent a nephrectomy. Harrison[4] in 1897 performed the first ureterostomy as we are familiar with it today. With improvement in technique, this method of urinary diversion was adapted to accompany cystectomies that were performed for carcinoma of the bladder.

Complications following cutaneous ureterostomy were constantly present, including abscesses, ureteral obstruction, chronic infection with or without renal calculi, and renal failure. The difficulty in achieving a good, workable stoma was continually present and a catheter was needed for drainage in all early cases. The management of cutaneous ureterostomies was difficult and associated with the blocking of catheters, the falling out of catheters, unpleasant odors present as a result of the urinary leakage, and poor collecting apparatuses available for use.

In the performance of cutaneous ureterostomy the ureter is usually exposed at its middle or distal third, the latter being preferable. A modified McBurney incision or the Gibson incision, which curves downward to the symphysis from the anterior superior spine, can be used. After splitting the muscles or incising them, the transversalis fascia is sectioned and the retroperitoneal space entered. The epigastric vessels can be retracted or ligated if necessary. The ureter is attached to the peritoneum and moves with it, a point frequently overlooked when looking for it in the depth of a wound. Care must be taken in freeing the lower end of the ureter from the peritoneum not to strip its adventitia too clean because it carries the blood supply. After transecting the ureter as close to the bladder as possible it is brought to the surface either through the operative wound or a smaller incision made to receive the anastomosis. One must bring the ureter out, avoiding angulation and allowing sufficient length to prevent undue tension.

The achievement of a good cutaneous stoma with absence of constriction or sloughing is difficult. Variations in methods of anchorage and forma-

tion of the stoma were frequently attempted. The most commonly accepted method was the incision of the distal tip of the ureter in two places longitudinally and "fishmouthing" the end, forming equal flaps to be sewed to the skin. Attempts were made to achieve eversion of the distal tip of the ureter on the skin to form a cuff. One method everted the distal end and built up a nipple-like skin flap on the abdominal wall. The ureteral tip frequently sloughed and there was a great tendency to stricture. There have been numerous attempts to produce a skin tube ostium and many examples of surgical skill and imagination have been reported but in most instances the use of a catheter was required. Several types of satisfactory skin appendages have been constructed and fitted to various drainage apparatuses. Fish and Stevenson[21] performed a two-stage procedure in this manner. Hudson et al.[25] reported a simplified one-stage procedure which they thought met all the requirements to assure a good stoma and prevent complications. The presence of scars, a colostomy or reaction of skin from radiation resulted frequently in placing the ureteral stoma in an area that was not a desirable site. Obese patients had more difficulty than thin ones and the placement of drainage cups frequently was a problem.

In May, 1962 a method of cutaneous diversion by Lloyd, Cottrel, Cross and Calams was reported.[33] This was called a high cutaneous ureterostomy. They recommended that the ureters be brought straight out to the skin by the shortest possible route. In this manner they eliminated dissection of the ureter from its bed with subsequent disturbance of the ureteral blood supply. The ureter remains essentially in its normal retroperitoneal environment without being subjected to pressure, stretching and kinking. The procedure is adaptable to normal and dilated ureters. They utilize the upper half or less of the ureter, bringing it out to the skin so that the ostium is in the anterior axillary line approximately midway between the line of the twelfth rib and the iliac crest. The end of the ureter is fishmouthed and directly anastomosed to the skin. A modified skin flap to help in the formation of a satisfactory stoma is used. A catheter is required for a few days after which a collection appliance is fitted.

In the presence of certain pathological states, there may be some advantages associated with cutaneous ureterostomies. However, the procedure fell more or less into disuse until the past five years, when emphasis was placed on avoiding the use of catheters and preventing constriction of the anastomotic site of the skin by so-called combined-single or double-barrelled stomas. Swenson and Smyth devised an operation used successfully in children with aperistaltic megaloureters.[44] In order to preserve the blood supply of the ureters and prevent stricture by the deep fascia, they "coned out" a tunnel for each ureter in the abdominal wall, through which the ureters ran obliquely. The muscle of the distal 2 cm. of the ureters was excised and the ends of the elastic mucosa were everted to anastomose to the skin and reduce the possibility of stricture. They achieved a bilateral

extraperitoneal cutaneous ureterostomy with the ostia side-by-side in the midline, midway between the umbilicus and symphysis, which functioned well without requiring catheters and was readily and easily cared for with a simple collecting apparatus. In 1961 Chute and Sallade[8] successfully adapted this method to a patient who had thickened, dilated ureters and carcinoma of the bladder. They performed a bilateral cutaneous ureterostomy, bringing both ureters out side-by-side through the middle of the operative wound, producing a so-called double-barrelled stoma. Following the removal of catheters which had been used to insure good urinary drainage in the immediate postoperative period, the patient did well, wearing a satisfactory bag for urine collection. The authors recommended this procedure as preferable for patients who are not obese and in whom a suitable length of ureter is available to bring to the surface.

These reports stimulated further work on the construction of double-barrelled cutaneous ureterostomies and the avoidance of intubation. Lapides[31] reported his method, indicated for use when the ureters are thick-walled and hypertrophied, and confirmed the reports of DeVries[16] and Humphreys,[26] who observed that hypertrophied ureters could be transplanted to the skin readily but normal ureters frequently were transplanted with difficulty. The Lapides procedure brought the ureter to the surface in adults through the peritoneum rather than extraperitoneally. He constructed what he described as a "butterfly cutaneous ureterostomy" because the immediate postoperative appearance of the wound resembled the wings of a butterfly. He achieved the effect by bringing the ureters to the skin's surface together in the midline, spatulating the ureteral ends and joining them together and then anastomosing the joined ureters to the skin in a transverse incision that had been developed with small skin flaps. Actually, the procedure involves a modified Z-plasty between the ureters and the skin after spatulation of the former. After satisfactory postoperative drainage the catheters are removed and the ureters function well with a good collecting apparatus.

Another supravesical cutaneous diversion prodecure was reported by Thompson and Ross.[45] They devised a common stoma with skin flap interposition, also utilizing a Z-plasty principle. They also applied their procedure to ureters in which some degree of dilatation was present, but were of the opinion that eventually the procedure would be readily applied to normal ureters. They anastomosed the medial margins of the spatulated ureters to form a common stoma. The ureters were brought to the midline in a curve, allowing for extraperitoneal approach to the skin's surface. The stoma was sutured to a skin flap that had been prepared in a manner that allowed interposition in depth of the skin flap, producing a stoma in which stenosis and intubation were avoided. Their results were good.

Higgins[23] in 1964 devised an ingenious placement of the cutaneous ureterostomy stoma to be used for shorter ureters. He produced a common stoma by suturing the medial borders of the incised terminal ends of the

ureters and performing the cutaneous anastomosis by utilizing the umbilical dimple as the site. His procedure is transperitoneal by means of tunnels constructed through the peritoneum and omentum to the umbilicus. He adjusts the tunnels anatomically to establish the most direct course from the kidney to the outside. His patients were able to maintain a catheter-free existence. The procedure worked well with cystectomy for carcinoma.

## INTERNAL URINARY DIVERSION

### Uretero-intestinal Anastomosis

Altering the course of urinary flow by some means of uretero-intestinal anastomosis was one of the earliest planned attempts to achieve diversion. These studies were stimulated by the fact that humans could adapt to cloacal arrangements resulting from trauma or complications of perineal surgery. The first successful planned procedure to attain this type of diversion was accomplished by John Simon[43] in 1851 when he created a ureterorectal fistula by use of a necrotizing suture through the wall of the ureter and adjacent rectum. In 1891 Kuester[30] performed a necrotizing suture procedure following a cystectomy for carcinoma of the bladder. Chaput[4] is credited with being the first surgeon to perform bilateral transplantation of ureters associated with cancer.

Technical interest centered on producing an anastomosis between ureter and bowel that would not constrict regardless of the area of the intestinal tract that was utilized. The most historically important breakthrough in this problem came with the work of Robert Coffey in 1911.[9] He applied his knowledge of submucosal anastomosis in the surgery of the bile and pancreatic ducts to create a tunnel anastomosis between the ureter and the bowel. He reasoned the procedure would prevent reflux by the establishment of a valvelike mechanism. After the abdomen is entered the parietal peritoneum over the lower ureter is incised and a portion of the ureter mobilized. The ureter is cut and its distal end ligated. The cut end is cut on a bias and a double-needled suture is passed through the tip. A small incision is made in the tenia, down to the mucosa of the sigmoid at a predetermined site. The mucosa is opened at the distal end of the trough made by the tenia incision and the tip of the ureter is inserted through the opening. A two-needle suture is now used to pass the suture through the bowel wall from within the lumen and the suture is tied on the tenial surface. The lower end of the ureter is laid in the trough and the edges are sutured over it through the ureteral adventitia. The parietal peritoneum is closed over the anastomosis area. Coffey subsequently modified his original technique two times so that his operations came to be known as the Coffey I, II and III procedures.[10, 11] In 1936 a report by Hinman and Weyrauch[24]

reviewed the history of ureterointestinal implantation and cited 60 different techniques that had been used to perform the anastomosis.

The age of antibiotics and chemotherapeutic agents introduced the next fortuitous environment for this operative procedure. It allowed better preparation of the bowel before surgery by cleansing and sterilization and prophylactic procedures postoperatively. The elimination or attenuation of infections reduced the incidence of stricture and breakdown at the anastomotic site. This led to what many consider to be the first milestone of improvement after Coffey, when Nesbitt[38] in 1949 and Cordonnier[12] in 1950 described a technique for direct mucosa-to-mucosa anastomosis of bowel and ureter. In the Nesbitt procedure the ureter was mobilized in the usual fashion and the distal end was spatulated to form an elliptical opening. The opening in the bowel was made through all layers into its lumen. The end of the ureter was anchored at each end of the bowel opening and the ureteral mucosa was directly anastomosed to the bowel mucosa by a continuous fine catgut suture. In the Cordonnier operation the ureteral end was not spatulated but cut across and anastomosed to an opening in the bowel by interrupted mucosa sutures. These procedures removed the hazard of constriction and ureteral obstruction, but reflux to the kidneys frequently developed as a complicating factor.

In 1952 Woodruff, Cooper and Leadbetter[49] and Weyrauch and Young[47] independently reported techniques of combining the elliptical mucosa-to-mucosa technique of Nesbitt with the Coffey tunnel procedure. Mathisen[35] introduced a method of constructing an intraluminal nipple for the terminal 2 cm. of the ureter from a full-thickness flap of intestinal wall. Nesbitt,[39] in reviewing his experiences with ureterosigmoid anastomoses, was impressed by the good health and long-term survival of several patients who had undergone a Coffey I procedure. On the basis of this review, he devised a procedure combining the Mathisen nipple with the Coffey tunnel and was satisfied with his early results.

ELECTROLYTE IMBALANCE. While many surgeons and patients still prefer uretero-intestinal anastomosis as opposed to constantly draining urine, others have questioned the ability of man to achieve acceptable life expectancy on a cloacal existence. This contention is based on the theory that accumulating urine in the bowel of a certainty results in the disturbance of body chemistry. Contrary to this opinion are the conclusions of others that in the absence of ureteral obstruction and renal impairment, or reflux with subsequent pyelonephritis, disturbances of a chemical nature will not occur. Despite the improvement in techniques and reduction of complications of urinary intestinal diversion, certain symptoms presented by many of these patients from one to several years after surgery attracted attention. They exhibited weakness, fatigue, anorexia, nausea, vomiting and diarrhea, dehydration, weight loss, lassitude leading to coma, and even death. These states were frequently considered due to the underlying disease process which necessitated the diversion in the first place.

The earliest indications that absorption from the bowel could have any significance was reported by Bollman and Mann,[3] who demonstrated that urea could be absorbed from a dog's colon after ureterosigmoidostomy. Jewett[28] in 1940 inferred that acidosis was related to chloride absorption from the bowel and he was successful in correcting the condition by the administration of a low salt diet and alkalies. The nature of the electrolyte disturbances was not appreciated until the report of Ferris and Odel,[20] which confirmed Jewett's impression. Their report on 141 patients with bilateral uretero-intestinal anastomoses demonstrated that 79 per cent had an elevated plasma chloride and decreased carbon dioxide combining power. The terms hyperchloremia and hyperchloremic acidosis became the accepted designation for the physiological states of these patients. Doroshow[17] reported acidosis was associated not only with absorption of chlorides from the colon but also the absorption of the urea and acids. Boyce and Vest[5] accounted for the association of azotemia with hyperchloremic acidosis by postulating that urinary ammonia was absorbed in ratio with chlorides not only from the kidney but also from the decomposing urea. In addition to the disturbances of sodium, chlorides, ammonia and bicarbonate, potassium imbalance is not uncommon as shown in the report of Jacobs and Stirling.[27]

A number of investigators postulated that renal impairment could be produced by the intracolonic pressure necessary to move the column of fluid resulting from the ureteral anastomosis. They considered renal failure an underlying factor causing acidosis. While the underlying mechanisms of hyperchloremic states have many theories, there are three accepted tenets: (1) the greater net uptake of chloride over fixed base from the colon, (2) impairment of renal function altering the tubular base-sparing mechanism, and (3) a combination of the two. Modern concepts agree that bicarbonate concentration in the colon is higher and chloride content lower than in the plasma. Changes in the acid-base equilibrium are associated with the exchanges of the ions of these substances in combination with the production and absorption of ammonia.Potassium concentration is high in the bowel, probably related to the active transport of sodium ions as well as the secretion of potassium. Acidosis may result from absorption from the colon, renal impairment or a combination of both. Creevy,[14] in a review in 1953, concluded that four factors played a role in the production of electrolyte imbalance: (1) the surface area exposed to urine, (2) the frequency of emptying of the bowel, (3) the segment of bowel involved, and (4) the functional capacity of the kidney.

**Ileac Conduits**

The collected data with respect to the chemical imbalance and gradual deterioration of patients with urinary intestinal diversion stimulated constant investigation for refinement. The significance of electrolyte

imbalance revived interest in the fabrication of a conduit rather than a reservoir to accomplish urinary discharge. A portion of the ileum was accepted as being the best suited because of its accessibility, blood supply and peristaltic activity. Successful isolation of a segment of ileun and anastomosis of ureters to it had been demonstrated as early as 1888 in dog experiments by Tizzoni and Foggi.[46] In 1950 Bricker[6] deliberately used an isolated segment of ileum as a urinary conduit while performing pelvic evisceration. The operation can be accomplished by isolating a section of ileum about 6 inches from the ileocecal valve, its length depending on its blood supply. The loop and its mesentery are placed below the reanastomosed intestine. The ileum is closed at one end, preserving the proper peristaltic direction. The ureters are dissected free as low as possible through small incisions in the parietal peritoneum and anastomosed to the ileal segment near the closed end. Care must be taken in bringing the left ureter under the colon retroperitoneally, to prevent kinking. Anastomosis is by direct mucosa-to-mucosa technique, with a good button of bowel mucosa removed to prevent stricture. The open end of the loop is brought to the skin surface at a preselected location. A button of fascia is generously removed also to prevent stricture. The mucosa of the loop is everted and sutured to the skin. The loop is secured to the peritoneum before closing the abdomen.

The paucity of reports of utilization of the small bowel as a conduit for urine prior to 1950 demonstrates the failure of individuals to appreciate that perhaps the electrolyte imbalance may have been associated with the length of the segment and total area of intestinal mucosa available for absorption. Bricker[7] reported his experiences with 150 uretero-ileal anastomoses in 1956 and stated that hyperchloremic acidosis was not seen in his series. In 1960, Cordonnier and Nicolai[13] analyzed 215 cases of ileac conduit diversion. It was their impression that the isolated ileal segment was superior to all methods used previously. They concluded that acidosis, when it did occur, was frequently associated with pre-existing severe renal damage. Creevy[15] in 1960 reviewed a series of patients who underwent ileac diversions, and reported a fairly high incidence of acidosis. Granting that his patients were considered poor risks and had pre-existing impairment of kidneys and ureters prior to surgery, he concluded: (1) Hyperchloremic acidosis can follow ileac diversion. (2) Pre-existing renal disease and thin-walled, dilated ureters predispose to the complication, while stenotic stomas can cause or aggravate it.

The size of the mucosal area or surface exposed to the presence of urine is a prime factor in the production of acidosis. In the ileal segment with active peristaltic action, the low intraluminal pressure and the relatively empty state of the conduit preconcludes a low incidence of acidosis. The lengthy redundant segment can predispose to greater absorption of urinary elements.

## MISCELLANEOUS TYPES OF DIVERSION

There have been a variety of methods for urinary diversion reported, in addition to those we have discussed. Many are entirely successful in the hands of their originators or modifiers, and may eventually prove more advantageous. An isolated ileocecal pouch with ureters transplanted to the cecum was reported by Gilchrist and Merricks.[22] This substitute bladder was formed by isolating the cecum and a segment of ascending colon containing several inches of terminal ileum. The end of the ileum was brought to the outside as an ileostomy. The pouch was emptied periodically by catheterization. No drainage apparatus was required and renal infection and acidosis were evidently not a problem in the patients so handled.

Also representing these miscellaneous operations are urinary diversions accomplished by means of an isolated rectal segment, combined with abdominal colostomy. This was first performed in animals by Mauclaire[36] in 1895. Pyrah[41] recommended the procedure in 1957 and in 1961 Dorsey and Barnes[18] reported several cases. By isolating a section of rectum with ureters anastomosed to it, the patient has voluntary control of urine, although there may be some leakage during sleep. The colostomy requires the usual care. This procedure affords a smaller mucosal surface for absorption of urinary elements from the bowel and requires lower pressures to empty itself. Hyperchloremic acidosis in patients with ureterosigmoidostomy can be corrected by converting the diversion into a rectosigmoid bladder and performing a proximal colostomy according to Wilkins and Wills.[48]

Hinman and Weyrauch[24] cited the diversion Gersuny accomplished in 1898 when he fabricated a rectal bladder and brought the proximal sigmoid colon out anterior to the rectum through an opening within the anal sphincter. In 1953 Lowsley and Johnson[34] reported the modified Gersuny, Lowsley-Johnson procedure which provided separate orifices for urinary and fecal discharge with voluntary control. Johnson[29] reported a series of patients in 1956 who were continent and had a low incidence of pyelonephritis and electrolyte imbalance. This is a complicated, technically difficult procedure and all continence is lost if the anal sphincter is damaged, which frequently occurs.

Finally, we have several attempts at anastomosing an isolated segment of ileum, to which the ureters have been joined, directly to the posterior urethra. A large enough ileal loop is devised to form a so-called artificial bladder. Mellinger and Suder reported such a procedure which proved satisfactory in isolated instances.[37] There have been other reports of similar utilization of ileum and urethra but some objections have been voiced because a portion of urethra and prostate gland is used that should be removed in performing a total cystectomy. Here again, the larger area of bowel segment utilized may be conducive to malabsorption and electrolyte imbalance.

## SUMMARY

The ingenuity of modern investigators will no doubt produce a method of diversion that will lend itself readily to all situations and fulfill all requirements for patient satisfaction and normal physiological maintenance. Diversion of the urine by permanent nephrostomy is the least desirable method in treatment of bladder carcinoma by cystectomy, since a catheter is required and, even under optimum conditions of care, infection is present in the majority of patients. Periodic replacement of the catheters is necessary and associated complications frequently occur. If catheters come out accidentally and are not replaced as soon as possible, there may be difficulty in replacing the tube. Notoriously, the opening of the sinus tract contracts and within 24 hours one may have difficulty locating the tract to the kidney.

Cutaneous ureterostomies that avoid the use of permanent catheters are acceptable. Here the double-barrelled or combined stoma seems very promising but does not eliminate the need for a collecting appliance. In obese patients, any cutaneous diversion presents problems but the prevention of acidosis by external diversion may well overcome objections to the procedure. A comparison of patients with permanent nephrostomy and permanent cutaneous ureterostomy demonstrates that complications of the ureterostomy are less troublesome than those of the nephrostomy.

Ureterosigmoidostomy has been and still is a widely used diversionary procedure and finds many supporters. The increasing incidence of acidosis, however, has convinced most urologists that the conduit procedure is today the method of choice for diversion, not only in carcinoma of the bladder but in many neurogenic and congenital conditions, and is superior to all previously used methods. At the present time, however, considering complications, the choice of diversion often lies between the use of the cutaneous ureterostomy with the double-barrelled stoma, and a well executed, carefully planned conduit procedure.

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# Traumatic Cord Bladder: Management and Complications

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By the time this communication is published, nearly two decades of experience with the management of the traumatic cord bladder at the Veterans Administration Spinal Cord Injury Center at Long Beach, California will have been reached. This experience includes over 2000 paraplegic patients seen at our center; this number does not include the patients seen on our charity and university services. During this period patients at our center, as well as in most schools in the world, have had an indwelling intraurethral catheter introduced at onset of injury;[2, 4, 10, 16, 20, 30] yet, every effort has been made to rid the patients of this catheter as soon as possible. Admittedly, the majority of patients so treated have urinary bacilluria even after they become catheter-free.[1, 4, 10, 12, 30] The presence of infection has led others to find methods of initial therapy that might avoid the complications attributed to the catheter and/or infection, namely, intermittent catheterization,[18, 25, 31] ileal conduits,[8, 14, 28] ileocystoplasties,[15, 17] cutaneous vesicostomies,[23, 24] therapy based on metabolic concepts,[21] muscle and nerve electrical stimulation[3, 9, 19, 22, 27] and suprapubic needle aspiration.[29]

It is not the purpose of this paper to discuss the pros or cons of the above listed procedures,[13] but rather to relate the established method of treatment that has been used to date at our center. Understandably, in the various centers in the United States treatment varies somewhat; the stress on certain phases of treatment differs. In common, however, is the initial introduction of an intraurethral indwelling catheter. Only time will tell whether one or a combination of the above enumerated procedures will supersede our present method.

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## DIAGNOSIS

An understanding of the importance of the conus medullaris, which contains the sacral segments of the spinal cord, is mandatory before one can appreciate the type of bladder that will result from a lesion at a particular level in the spinal cord; the conus medullaris contains the spinal integrating reflex centers for micturition.

Both the autonomic pelvic nerves and the somatic internal pudendal nerves emanate from the conus medullaris. Afferent and efferent fibers to and from the detrusor are contained in the pelvic nerves (nervi erigentes), whereas sensory and motor fibers to and from the striated muscles of the pelvic floor course in the internal pudendal nerves. An understanding of the reciprocal relationship of these two nerve pairs quickly resolves the mysticism displayed by many physicians concerning the traumatic cord bladder. If the orthosympathetic system plays a role at all in micturition, it is negligible from a therapeutic standpoint. For practical purposes the autonomic nerves (pre- and post-ganglionic) are considered as if they were a single unit, i.e., a lower motor neuron, comparable to that of the somatic pudendal nerves.

The type of bladder that will result following injury to the spinal cord will depend on the location of the lesion; namely, whether it is in the spinal cord above the conus medullaris or whether the lesion is at or below the conus medullaris, i.e., the conus medullaris and/or cauda equina (Fig. 1). If the conus medullaris and its roots are undamaged, the reflex patterns through the pelvic and internal pudendal nerves are intact; this is called an *upper motor neuron bladder*.[4] If the conus medullaris or its peripheral nerves are damaged, the reflex patterns through the autonomic and somatic nerves are absent; this is called a *lower motor neuron bladder*.[4] A third but very small group occurring among patients with spinal cord injuries is known as the *mixed motor neuron bladder*.[4] Two types are usually found in this last group: (1) reflex activity is present by way of the internal pudendal nerves but absent through the pelvic nerves; (2) reflex activity is absent through the pudendal nerves but present through the pelvic nerves.

Diagnosis of the type of bladder is important for a rational regimen of treatment. Basically, one must know whether reflex activity through the various pathways connecting the urinary bladder and spinal cord are present. The "ice water test"[4] is performed in order to ascertain whether reflex activity is intact along the pelvic nerves from the bladder to the conus medullaris and back. In order to ascertain whether reflex activity is intact by way of the internal pudendal nerves, the following tests are performed: rectal external sphincter tone, bulbocavernosus reflex, and the anocutaneous reflex. Only by periodic testing from the time of injury can this be ascertained. Urological examinations, e.g., sphincterometry, cystometry, cystourethrography and cystoscopy, are adjuncts; a specific diagnosis can be made only by the neurological tests.

A neurological examination is part of any standard physical examination. From this examination we ascertain whether the neurological lesion is complete or incomplete. Obviously, incomplete lesions may be so incomplete as to be nearly normal, functionally speaking, and demonstrate, at most, slight precipitate micturition; on the other hand, the incomplete lesion may be nearly a complete lesion for practical purposes.

The necessity of a good tentative diagnosis by a detailed history before resorting to the laboratory and physical examination holds true even for the traumatic cord bladder. Once the patient is catheter-free, the mode of voiding will act as an aid in classifying the type of bladder, especially among patients with complete neurological lesions. The patient with a typical upper motor neuron bladder will state that his bladder generally ejects its contents spontaneously (reflexly) by detrusor contraction, which can be elicited by strain, Credé pressure to the bladder, tapping the suprapubic area, pulling the pubic hair, hitting the thighs, and/or stimulating the external rectal sphincter digitally, etc. Patients with lesions

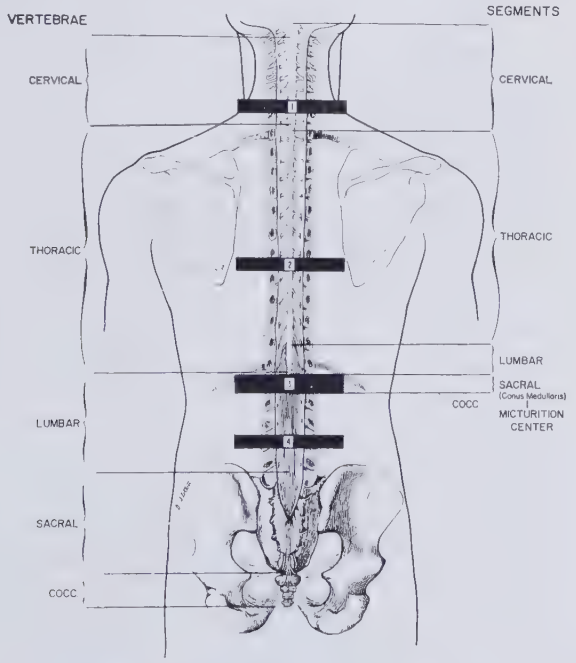


Figure 1. Relationship of the spinal cord micturition center and the vertebral column. The spinal cord (tip of the conus medullaris) ends approximately between L1 and L2 vertebra. The dura mater ends between S1 and S2. The sacral segments of the conus medullaris are the reflex integrating centers for micturition. Lesions above the conus yield upper motor neuron bladders (for example, lesions number 1 and 2 in the above drawing), whereas lesions at or below the conus yield lower motor neuron bladders (for example, lesions number 3 and 4 in the above drawing). (Reprinted from the author's article in British Journal of Urology, *31:* 1–46, March, 1959, by permission of the Editor, Mr. David Band.)

above the splanchnic outflow may describe symptoms of autonomic dysreflexia, namely, bradycardia, sweating of the forehead, cutis anserina, nasal obstruction, pounding headache and hypertension, which disappear as soon as the bladder begins to empty. Other than by occasional paradoxical inhibition,[4] the stream of the upper motor neuron type of bladder cannot be stopped once initiated. Per contra, the patient with a typical lower motor neuron bladder will state that he can empty his bladder by sustained extrinsic pressure, i.e., strain or Credé; upon release of this extrinsic pressure the stream will stop (passive inhibition). The tentative diagnosis made by history can very quickly be confirmed by the neurological tests.

If the patient displays somatic spasticity below the level of the lesion, one may assume that the lesion is in the spinal cord per se and consequently above the conus medullaris with a concomitant upper motor neuron bladder, e.g., lesions number 1 and 2 in Figure 1.[10] A patient with a somatic flaccid paralysis below the level of the injury, including the lower extremities, may have a lower motor neuron type of bladder, but this can be misleading; for example, a lesion either in the lumbar segments of the spinal cord or its roots may yield a flaccid paralysis of the limbs but result in an upper motor neuron type of bladder (epiconal lesion). Consequently, the importance of performing the neurological tests becomes self-evident. Rarely injuries of the midthoracic segments of the spinal cord are found which cause a somatic flaccidity (permanently) because of a descending degeneration of the cord, possibly on a vascular basis, by thrombosis of the vessels supplying the spinal cord. These patients in turn will also have a lower motor neuron type of bladder (Fig. 2). The highest level that I have seen in this respect was at the sixth thoracic dermatome.

The foregoing discussion has presented the typical situations found among the vast majority of our patients. Occasionally, equivocation may arise as to the type of bladder we are treating. The astute physician will use supporting measures to categorize more accurately the condition of such a bladder; e.g., the residuum-capacity test, sexual function, bowel function, tests of mucosal bladder sensation, or electromyography.

During the catheter-bound bladder stages following injury, the diagnosis depends upon the neurological tests. There are no tests easier to perform or more quickly accomplished than these. In fact, no additional tests are necessary (for most bladders) than those used during any physical examination. Any physical examination performed by a physician irrespective of his specialty is not complete without a digital rectal examination; this latter examination not only seeks out rectal or prostatic pathology but allows simultaneous determination of the presence or absence of external rectal sphincter tone. An additional brisk squeeze of the glans penis will ascertain whether the bulbocavernosus reflex is or is not present. If it is present, we can assume that conduction of sacral reflex arcs along the internal pudendal nerve is intact and, by inference, assume that this is

also true for the pelvic nerves. Such was our assumption prior to the introduction of the ice water test; it has been found valid in the majority of patients.

Bors uses the ratio of residual over capacity as a percentage; 0 to 20 per cent (based upon 250- to 300-ml. capacity) is considered compatible with upper motor neuron bladders (reflex voiding), whereas 0 to 10 per cent (based upon 300- to 400-ml. capacity) is compatible with lower motor neurons (voiding by Credé or strain). If the above-mentioned percentages are present, Bors calls the function of these bladders "balanced." If residual urines exceed somewhat these percentages, yet the patient remains clinically well without a catheter, i.e., without fevers and with good excretory urograms, he may be permitted to go on without a catheter if closely observed. On the other hand, if with this same residual the patient is not well or shows pyelographic deterioration of the kidneys, he is not ready to part with his catheter. A few patients may have excellent kidneys but become febrile when left without a catheter, in spite of a zero residual and no demonstrable vesicouretral reflux with cystograms. We permit this small group to retain their catheters.

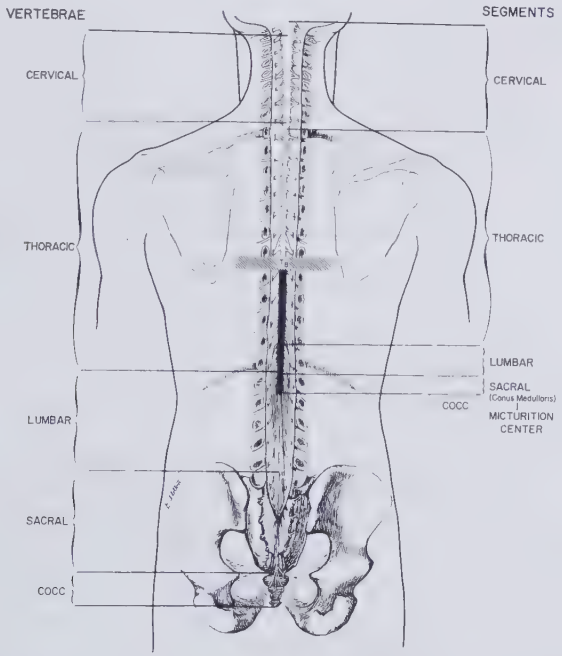


Figure 2. Degeneration of the spinal cord. Degeneration of the spinal cord (black area of the cord in the above drawing) occurs occasionally below the level of injury. The patient remains permanently areflexic somatically below the level of injury and will have a lower motor neuron bladder. (Reprinted from the author's article in the British Journal of Urology, *31:* 1–46, March, 1959, by permission of the Editor, Mr. David Band.)

## BASIC MANAGEMENT OF THE BLADDER

Treatment during the first year following injury is as follows.[11] As soon after injury as possible a size 16 F. Foley bag catheter is inserted. The catheter is taped to the abdomen in order to straighten the penoscrotal angle in an attempt to prevent periurethral abscess with subsequent diverticulum and/or fistula.

Following introduction of the catheter, the rubber catheter is hooked up to a closed irrigation system, the tubing of which is made of plastic material. The most dependent tubing is connected to a bottle suspended from the bedframe; staphene is instilled into the bottle for sterilization purposes. The patients remain on straight drainage, except for bladder irrigations three times a day through the closed irrigation system, until their general condition is well stabilized, including the postoperative period following a possible laminectomy. Once it is stabilized, excretory urography and cystourethrography are performed. Both tests serve as baselines for future comparisons. If there is no evidence of vesicoureteral reflux of such magnitude as to warrant a pyelogram, bladder training is started and maintained until a balanced bladder function is attained (or indefinitely if this goal is not achieved). Bladder training is also used among patients with lower motor neuron bladders for the regulated intake of water and for psychological reasons.

Bladder training alone is used for patients with lower motor neuron bladders. In addition to bladder training, the blocking procedures with anesthetic agents are used for patients with upper motor neuron bladders.[4, 5, 6, 7, 10, 11, 26] Bethanechol (Urecholine) is used in patients with upper motor neuron type of bladders whose lesions are neurologically incomplete; our experience to date indicates that it is ineffective in patients with complete lesions, even in dosages which cause side effects. As yet we have not found a parasympathicomimetic drug that is reliably effective in patients with neurologically complete lesions.

Usually no type of surgery to achieve bladder function is attempted before one year or more has elapsed since the injury. This delay is justified by the fact that about two-thirds of the patients who become catheter-free spontaneously do so within six months following injury and the remainder within one year or even more. If a catheter-free state has not been attained at the end of one year in a patient with a lower motor neuron bladder, a transurethral vesical neck resection is indicated. Occasionally, resections have to be repeated. As a last resort, partial resection of the external urethral sphincter by internal electro-excision may become necessary.

If a patient with an upper motor neuron type of bladder has not regained a catheter-free state at the end of one year, the therapy depends on a variety of factors. Provided that the patient had responded to pudendal nerve anesthesia, albeit temporarily, and has no reflex erections, pudendal neurotomy may be indicated; in those patients with erections, we prefer

an anterior vesical neck resection, which has proved successful. Patients who responded, although only temporarily, to selective sacral nerve anesthesia may be considered as candidates for selective sacral neurotomies. Should the patient not be suited for any of the neurotomies, a vesical neck resection is indicated; if this fails, a partial transurethral resection of the external urethral sphincter may be attempted. Combinations of neurologic procedures (anesthesia, neurotomy) with urologic procedures (resection) should not be overlooked. Whereas a pudendal block of itself, for example, may not bring the desired result, repeated pudendal nerve anesthesia following an apparently unsuccessful transurethral resection may hit the "trigger."

## RESIDUAL URINE TESTS

Since we cannot foresee when a balanced bladder function will occur in any one patient, we perform residual urine tests weekly once the condition of the patient is otherwise stabilized. The capacity-residuum test is then performed as follows: (1) the patient drinks one glass of water hourly beginning at 6:00 or 7:00 A.M. whether he is catheter-free or catheter-bound; (2) as soon as he seems adequately hydrated, the contents of the bladder are drained and the catheter is removed.

The patient with a typical upper motor neuron lesion notifies the person performing the test at once after a fair amount of urine has been voided in one full stream into a urinal. Small, repeated "squirts" of urine must not be included in the total amount voided; such a test is worthless. Only the specimen ejected in a full stream, within an hour after the removal of the catheter, is to be measured, whence the technician proceeds at once to perform the following maneuvers in an attempt to reduce the residual urine: (*a*) tapping the suprapubic area, (*b*) stroking the thighs, (*c*) pulling the pubic hair, (*d*) squeezing the glans penis, (*e*) tapping the perineal area, (*f*) strain, (*g*) Credé pressure and (*h*) stimulation of the external rectal sphincter digitally. The additional amount of urine collected by any one or all of these maneuvers is measured separately and added to the amount of the spontaneously voided specimen; together they are the sum total of voided urine. Only thereafter is the catheter introduced to remove the residual urine. If the patient has not voided spontaneously at the end of one hour, the stimulation maneuvers, as listed above (*a* through *h*), are performed. If these yield a specimen, it is measured and then the residual urine is determined by catheterization.

The patient with a typical lower motor neuron bladder is instructed to strain and/or apply Credé pressure to his bladder for one hour, when the technician returns. The voided urine is measured. Then the catheter is introduced and the residual urine is measured.

Experience has shown that a waiting period of one hour will safely

avoid overdistention of the bladder; however, the waiting period may occasionally have to be extended to 1¼ to 1½ hours. All drugs, such as methantheline bromide (Banthine), atropine, hexamethonium and bethanechol (Urecholine), must be discontinued at least 24 hours prior to the test; only then can a true residuum be determined, uninfluenced by drug therapy. If a patient displays symptoms of autonomic dysreflexia, the residual urine test may have to be discontinued before the one-hour period. Once the balance of bladder function has justified a trial without catheter, the physician is still obliged to follow the patient closely. Should there be any doubt regarding the patient's voiding ability, a residual urine test should be done at once. Imbalance of bladder function requires reinsertion of the catheter. Should fever follow the removal of the catheter, reinsertion is indicated until the patient becomes again stabilized. Once catheter-free, the patient usually uses a condom-type urinal.

## COMPLICATIONS AND THEIR MANAGEMENT

Complications of the genitourinary system can occur at any time from onset of injury. Those complications most frequently encountered by the physician will be discussed.

### Penis

Good hygiene of the penis is of paramount importance, especially when there is a redundancy of the prepuce. The patients, as well as the personnel who care for tetraplegics, should always reduce the prepuce over the glans penis after it has been retracted for cleansing the preputial sac. Severe inflammatory phimosis or paraphimosis is the usual indication for circumcision; a dorsal slit is performed in the acute stage and a circumcision when the inflammatory process has subsided.

In patients with a short penis, circumcision will aid toward retaining the "condom receptacle" since the corona will act as an anchor for the elastoplast band.

Excoriation of the skin of the penis from urine and/or the condom appliance is not uncommon. Exposure of the penis to air under a cradle in bed is the quickest method of cure. The patient voids into a urinal; the urinal rests over a sufficient number of absorbent pads should the stream miss the urinal.

### Testicles

Epididymitis is the most frequent complication. It occurs whether the patient is or is not catheter-free. It must be differentiated from the phlegmon of a penoscrotal abscess with extension to the right or left half of the scrotum.

Acute epididymitis is treated with a scrotal support, ice bags and

antibiotics. Routine early prophylactic vasotomies after injury are not performed; we cannot deny parenthood to those patients who with time may attain procreative abilities. Partial vasectomies, as well as epididymectomies, are performed as interval operations on patients with recurrent disease. A large phlegmon may cause necrosis not only of the epididymis but also of the testicle, with spontaneous drainage through the skin; this usually requires epididymo-orchiectomy.

**Urethra and Bladder**

*Benign pseudopapillomatosis* (polyps) due to catheter irritation can be found anywhere on the mucosal lining of the urethra and bladder. These lesions are infrequent in the urethra, but they are frequent in the trigonal area and the bladder neck. Biopsy is indicated even though histological reports to date have been negative.

The insertion of a whistle-tip catheter, held to the penis with a four-prong halter, avoids the irritation of an inflated Foley bag and gives good results. Continuous irrigations with medicated solutions, e.g., silver nitrate 1:10,000, through a two-way whistle-tip catheter is very helpful in polyps both of the urethra and the bladder.

*Neoplasms of the urethra and bladder* have occurred among our patients; again the importance of biopsies is stressed.

*Diverticula of the bladder*, originating from cellules, are usually multiple and surgical therapy to date has not been indicated.

*Penoscrotal diverticula and fistulas* are due to the constant irritation by the catheter at the penoscrotal angle; many patients will develop periurethritis and abscess formation. A severe abscess or phlegmon requires incision and drainage, but not necessarily diversion. A small periurethral abscess at this site in a catheter-bound patient can be irrigated per urethra and its contents can be expressed periodically through the distal urethra. The introduction of a catheter is justified if a patient has a similar abscess but is catheter-free, and he is treated similarly. In both patients the catheter acts as a wick. Incision and drainage become, of course, necessary at the first clinical signs of sepsis.

Urethrography is essential before treatment is started. The mere presence of a diverticulum and/or fistula poses no indication for diversion. At this center we have instructed our patients with diverticula to empty the contents of the sac by manual pressure whenever the bladder empties, irrespective of the type of voiding, or to do the same at regularly spaced intervals if a catheter is present. Only when the diverticulum reaches such size as to become prone to recurrent abscess formation or to become generally unmanageable, do we consider surgery. We have adopted this policy since we observed that diverticulectomy, without diversion of the urinary stream, may result in fistulas or recurrent diverticula at the site of repair.

The sequential order of therapy of penoscrotal fistulas depends on whether or not the patient has a well-balanced bladder.

For the patient who has a well-balanced (catheter-free) bladder the following procedure is attempted: The tract is first mildly electrofulgurated if it has been present for some time. The patient is kept at bed rest until the fistula is healed. He must be turned every two to three hours day and night to both sides and supine, but never prone, in order to prevent pressure upon the urethra. No urinary receptacle must be attached to the penis, be it the "condom urinal" or a commercial urinal. The penis is surrounded with ample absorbent material, such as abdominal pads, and a urinal is positioned at the distal end of the penis to catch the urinary stream from the external urethral meatus. Much of the urine will be collected in the pads especially from the fistulous leakage in the early stage of treatment. The pads must be changed as soon as the patient notices that they are wet; an attendant must supervise this care in a tetraplegic patient. Up to three weeks are required before this technique achieves healing.

This method may be unsuccessful if the fistula is associated with a relatively large diverticulum as noted on urethrography. If this "pad-urinal" treatment fails in a patient with a balanced bladder, surgical treatment is attempted using the catheter as a splint. As soon as the skin wound appears healed, the catheter is removed and the patient is placed on the "pad-urinal" regimen. When it is certain that the result is good, the patient is advised to make every attempt to retain the "condom receptacle" solely by skin cement, since the elastoplast binder with its constriction of the urethra may be one of the etiologic factors, if not the only one, in a possible recurrence.

Obviously, this "pad-urinal" treatment is unsatisfactory when the defect of the urethra is of such size as to bare the catheter. Such a large defect should be first closed surgically with an intraurethral catheter as a splint.

We have stated from the very onset of our work in this field that every effort should be made to create a catheter-free (balanced) state before attempting closure of a fistula. If a catheter-free state cannot be achieved, surgical closure is performed without diversion if electrofulguration has failed. As a last resort for this latter group, suprapubic cystostomy was performed in the past. For persistent and/or recurrent fistulas we have attempted the use of penoscrotal urethrostomy; the results to date are satisfactory, but the follow-up time is rather short.

An occasional fistula has closed spontaneously in the past in spite of an intraurethral catheter; thus, one need not rush into surgical closures.

*Bladder calculi* will develop in over 50 per cent of patients during the bedfast period. A closed irrigation system using Suby's "G" solution or Renacidin should either prevent the formation of stones or prevent them from reaching such sizes as would prohibit lithotripsy. If patients are

closely followed, once discharged, cystolithotomies or even lithotripsies seldom need be performed.

*Perineal urethral diverticula* follow bilateral ischiectomy. This complication should not be seen frequently if the admonitions are heeded concerning the closure of ischial ulcers. Introduction of an intraurethral catheter in patients with this complication has averted further difficulty, namely, the development of a urinary fistula at the ischiectomy site. Diagnosis is verified by cystourethrography.

Difficulty in inserting a catheter past the vesical neck is a pathognomonic sign of a *subtrigonal diverticulum.* Although some of these diverticula probably occur spontaneously, they are aggravated by the constant "spearing" of the catheter, which tends to take the wrong route. Other subtrigonal diverticula are the result of overenthusiastic transurethral resection of the posterior vesical neck lip.

Most of these diverticula can be removed by simple transurethral electro-incision of their roof. Suprapubic cystostomy may occasionally be indicated if the diverticulum appears to lie under a ureteral orifice, making electro-incision dangerous. Electro-incision may occasionally be indicated under vision through a suprapubic cystotomy.

*Vesicoureteral reflux* is found in both upper and lower motor neuron types of bladders, but more often in the former. We have not performed operations to correct this complication at our center because its pathologic physiology is still poorly understood. Our two main objections to operation would be: (1) we have seen patients with recurrence following operations done expertly elsewhere; (2) we do not know the exact time when to operate. The latter objection is readily appreciated from the following observations: in some patients reflux occurs early (practically at time of injury), in others many years after injury; on one day reflux may ascend midway into the ureter, on another it may be entirely absent; reflux may vary but is not consistent with bladder volume and intravesical pressure—at one time it may be bilateral, at another time unilateral; some patients have severe renal involvement, others do not. All these phenomena and variations can be found irrespective of age of the patient, level, extent and age of injury.

Subarachnoid alcohol injections, sacral extradural neurotomy, pudendal neurotomy, rhizotomies and spinothalamic tractotomies have no proven influence on vesicoureteral reflux; the indication for these procedures should not be based on the status of reflux.

The cystoscopic appearance of the ureteral orifices and bladder, whether associated with diverticula or not, is not necessarily pathognomonic for reflux. A severely malcontoured bladder may show no reflux, whereas a smooth bladder may.

Our experience to date does not suggest that reflux is aided by transurethral resection.

Because of the many variables associated with reflux and the definite

lack of indications for operative intervention, we have adopted the following policy. In patients with pyelographic reflux, unilateral or bilateral, with evidence of kidney damage or progressive renal dysfunction by excretory pyleography, we institute straight catheter drainage. If reflux is present in patients who are on catheter drainage, this is continued. The hydronephroses and kinked hydroureters usually show a remarkable recovery, and the catheter drainage attempts to impede further renal damage. Patients with normal appearing excretory urograms are continued on a regimen to render them catheter-free in spite of reflux, but are closely observed. The same holds for catheter-free patients; they, too, are permitted to go without catheters as long as there are no signs of kidney changes.

The presence of a catheter assures us of one factor: the patients usually do well clinically.

In attempting to cure one complication, one always must be on the alert to prevent another of even greater magnitude. Therapy of vesicoureteral reflux by straight catheter drainage creates the danger of contracture of the bladder, especially among patients with upper motor neuron lesions; but, fortunately, not in all patients. The presence of reflux prevents us from using bladder training as a counteracting measure. It is important to do residuum-capacity studies periodically; but one must also realize that in cases with severe reflux and hydronephrosis, testing of the capacity may become valueless, owing to the formidable capacity of the ureters and kidney pelvis.

Drugs such as Banthine and hexamethonium should be used in such cases, and when they fail to prevent or arrest the shrinkage of the bladder, subarachnoid alcohol injection or anterior rhizotomy must be considered to destroy the reflex activity through the sacral segments.

**Hydronephrosis**

If hydronephrosis is associated with vesicoureteral reflux, a regimen with straight catheter drainage usually suffices, provided there is no ureteral obstruction as from kinks or calculi.

Occasionally, hydronephrosis can be found with normal appearing upper urinary passageways and without demonstrable reflux. Even these kidneys have responded well to straight catheter drainage.

When hydronephrosis does not decrease following operative correction of obstruction or straight catheter drainage, urinary diversion must be considered. Depending on the situation, we have performed nephrostomies, pyelostomies, nephropyelostomies and cutaneous ureterostomies rather than nephrectomies. Since one is never certain of the future of the other kidney in a patient with a spinal cord injury, ultraconservatism is imperative. It is our clinical impression that the early reintroduction of catheters into "catheter-free" bladders at the first sign of kidney regression diminishes the future incidence of hydronephrosis. The goal can be achieved only by regular and close supervision of the renal status.

### Renal Calculosis

Infection plays a prominent role in calcinogenesis and is difficult to eliminate. In spite of early ambulation and adequate fluid intake, stones are forming in patients who have been injured for even as long as 15 or more years.

We have been unable to find good prophylactic measures to prevent stone formation. Until it was removed from the market we had a 60 per cent cure rate using 10 per cent Renacidin solution. Calculi are surgically removed as in any other patient. Operations for recurrent renal calculosis offer a greater possibility of ureteropelvic junction stricture; plastics are usually not satisfactory and permanent nephrostomies or pyelostomies must be considered.

## SUMMARY

In the foregoing paragraphs we have briefly related our present concepts of classification and diagnosis. The basic management of the traumatic cord bladder and its complications has been described as practiced over the past two decades at the Veterans Administration Spinal Cord Injury Center at Long Beach, California. With additional experience with those methods of early management listed in the opening paragraph of this communication, the basic therapy may remain the same, be modified or be essentially changed. Perhaps another decade of experience should bring us closer to the answer.

Since two-thirds of our patients initially treated with an indwelling catheter become catheter-free within six months and the remainder within a year and since, per contra, those patients given intermittent catheterization achieve a balanced bladder function within 70 days,[25, 31] the latter method may eventually become the method of choice in the initial and early management. Additionally, it is my feeling that with intermittent catheterization penoscrotal complications should be negligible. The more radical measures will probably have a place in the armamentarium of the urologist, but the proponents of these methods must eventually offer more specific indications.

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# Priapism

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The term priapism is an eponym derived from ancient Greek religion and mythology pertaining to the god Priapus, symbol of fertility. It has been reported that incantations to this god were accompanied by orgiastic rites.[1, 9]

Priapism is the prolonged and persistent erection of the penis which may occur without sexual stimulation. It is usually painful and becomes self-perpetuating after a given period of time.[13, 21, 29] There are accounts of cases in which the physiologically erect penis fails to return to the normal flaccid state and ultimately exhibits characteristics of genuine priapism.[8, 13, 32] The significant point is that deturgescence of the penis does not occur spontaneously.[40]

"Primary" priapism refers to a pathological erection not accompanied by disease which could cause or maintain erection, as distingushed from "secondary" priapism caused by factors directly related to or indirectly affecting penile reactivity. Cases in which sexual activity is incident to the onset of priapism might be considered primary priapism since they are pathological extensions of normal erections resulting in irreversible changes which prevent deturgescence.[20] "Idiopathic" priapism applies to cases without psychic or physical sexuality, with no secondary factors contributing to its occurrence and with no etiological or underlying pathological conditions apparent.[28]

## CLASSIFICATION

Many classifications have been designed for this condition.[20, 21] Since we have already defined primary priapism, secondary priapism, and idio-

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pathic priapism, the following classification will include all nosopoietic factors and is modified from that of Frank Hinman, Sr. and Frank Hinman, Jr.

A. **Neurogenic**
   1. Psychic stimuli
      a. Excessively prolonged or deviant sexual behavior resulting in genital overactivity, overstimulation, or overexposure to erotic stimulation. This is "primary" or psychophysiologic priapism (Case II).
      b. Fantasy syndromes and other aberrant mental states resulting in autoeroticism and priapism
   2. Direct central nervous system stimulation
      a. Multiple sclerosis, tabes dorsalis, injuries of the cervical cord, or other spinal cord injury; cases of strangulation which are not related to cervical cord injury (strangulation, suffocation)[1, 8, 26, 27, 30]
      b. Damage to certain parts of the cerebral hemispheres or lesions involving the medullary vasodilator center such as encephalitis or syphilitic meningomyelitis.[8]
      c. Neurologically active drugs such as strychnine and muscarine[1, 8]
      d. Vertebral tumors involving the spinal cord or vertebral tuberculosis
      e. Epileptic equivalents with priapism appearing as an equivalent of the epileptic fit. The priapism was reported to respond to treatment for epilepsy.[8]
   3. Reflex from local stimuli[1, 8, 24, 36]
      a. Phimosis with preputial calculi or with meatal warts or polyps
      b. Benign tumors in the fossa navicularis
      c. Urethral papillomas or polyps
      d. Ureteral or vesical calculus

B. **Chemical, Toxic, Infectious, Allergic or Inflammatory Conditions**
   1. Congenital syphilis with priapism in the newborn infant (rare)[20]
   2. Reaction to tetanus antitoxin (rare)[27]
   3. Complication of mumps (rare)[15]
   4. Poisoning by drugs, chemicals or aphrodisiac mixtures such as cantharides, yohimbin and turpentine, which may cause induration and engorgement of the corpus spongiosum (urethrae) in addition to bicorporal engorgement; also acute and chronic lead poisoning have been mentioned[1, 27]
   5. Carbon monoxide or carbon dioxide intoxication reported in well diggers[1]
   6. Hormones such as testosterone propionate[8, 27]
   7. Administration of hydralazine hydrochloride (Apresoline), an antipressor agent, reported to cause genital flushing and tingling with subsequent priapism[43]
   8. Tularemia,[11] typhoid fever or other bacteremias[27] causing pelvic thrombophlebitis (Case VII); focal suppuration leading to genital thrombophlebitis from systemic or local disease such as pelvic appendicitis, periurethral abscess or urinary extravasation from inflammatory disease[1, 8, 25, 36] (Case III)

C. **Mechanical or Traumatic**
   1. Hemorrhage or hematoma from trauma or degenerative disease or local vascular disorder such as:[1, 8]
      a. Straddle injury or injury to perineum[16, 38]
      b. Rupture of urethra or urethral stricture by instrumentation (Case IV)
      c. Direct injury to the penis or scrotum by external trauma; fracture of the penis;[38] genital thrombophlebitis or thrombosis from local trauma or mechanical devices[17]

d. Rupture of pelvic blood vessel or aortic aneurysm with retroperitoneal hemorrhage or obstruction of a large venous channel such as the vena cava[42]

2. New growths ("malignant priapism"[34]); these are cases of primary neoplasm of the penis and urethra or of metastatic infiltration or embolism of other tumors into the phallic area
   a. Secondary or metastatic tumor usually from prostate, bladder, testis, rectum, kidney and liver (in order of prevalence)[2, 6, 21, 34]
   b. Primary tumors of penis or urethra[22, 33]

D. **Hematologic** (estimated 20 per cent of cases of priapism)[38]
1. Chronic myelogenous leukemia, chronic lymphocytic leukemia, and chronic granulocytic leukemia[10, 18] (Case VI)
2. Sickle cell anemia[12, 19, 37, 39] (Case V)

## TREATMENT

The numerous methods of treatment for priapism have followed several general patterns, but the most universal treatment in the hands of most authors, and the most effective method of accomplishing detumescence, has been evacuation of altered blood from the corpora cavernosa. Review of the various methods of treatment reveals that relationship of treatment to the duration of the erection is the critical factor in successful detumescence of the penis and in maintenance of sexual potency. Age of the patient is also a determinant.

### Treatment of Secondary Priapism

1. Deep x-ray therapy to the penis for priapism associated with chronic leukemia.[4, 10, 23]

2. Systemic treatment for the leukemia and the priapism.[1, 18]

3. Resection of aortic aneurysm or correction of aortic-vena cava arteriovenous fistula in cases of rupture into the vena cava.[42] Other vascular surgery as indicated.

4. Treatment of systemic disease in cases of typhoid, tularemia, bacteremia or focal thrombophlebitis with expectant treatment of priapism.[11, 27]

5. Removal of local pathological excitatory stimuli such as urethral papillomas, polyps or phimosis.[1]

### Treatment of Early Primary or Idiopathic Priapism

The general principle applicable to the treatment of early priapism, and the justification for the conservative methods, is that the routes of venous egress may yet be patent at this stage, and the anatomical and pathological changes in the corpora have not become irreversible. The object is to restore venous drainage and to eliminate the possibility of progressive damage to the erectile mechanism. Sympathetic block would appear to be the incorrect procedure since it does not block, and may augment, the sacral parasympathetic (genital vasodilators) outflow which is responsible for erection under

normal circumstances.[20, 26, 41] It has been noted that operations on the lower urinary tract under spinal analgesia may be complicated by erections. The following treatment methods have been employed:

1. Enzymatic lysis of thrombosed blood in the corpora cavernosa.[42]
2. Use of anticoagulants systemically and/or locally.[16, 32, 38]
3. Administration of female hormones.[13, 16, 35]
4. Use of adrenocortical hormones.[36]
5. General or spinal anesthesia with sedation. (Hypotensive effect?)
6. Use of Arfonad (trimethaphan camphorsulfonate), a hypotensive agent, combined with general anesthesia and forcible massage or manipulation of corpora or aspiration of corpora.[5, 25, 32, 40]
7. Proximal ligation of unilateral internal pudendal artery.[7] This is a logical approach during early stage before changes have occurred within the cavernosal sinuses and during the stage of continuing arterial augmentation of the turgescence.
8. Administration of small doses of curare.[13]

**Treatment of Late Priapism**

At this stage, blood retained in the cavernous sinuses has become viscid, grumous or sludgelike.[20] The increased viscosity arises from elevated carbon dioxide tension of the sinusoidal blood causing chemical injury to the endothelium. The arteriovenous anastomotic channels then cannot regulate arterial inflow or permit egress of the venous blood (the dorsal vein of the penis has been found collapsed).[1, 20, 25] Conti has clarified the pathology of the erectile tissues. He showed that normal erection is controlled primarily by a series of muscular pillars protruding into the lumens of the arterioles, venules and arteriovenous anastomotic channels of the corpora cavernosa.[5] These pillars are under nervous control and will open and close these vessels. In the flaccid state the arterioles are partially closed while the venules and the arteriovenous anastomoses are open, thus permitting a small inflow of blood to the corpora and insuring good venous drainage. In the erect state the arterioles are fully opened while the venules and the arteriovenous shunts are partially closed, thus inflow is augmented and drainage is limited.[14]

The following treatment methods for late priapism generally interfere with the competence of the erectile mechanism, this effect being additive to the changes which have occurred within the venous sinuses resulting from edema, inflammatory changes, and endothelial injury with ultimate fibroplasia, thus limiting the ability of the erectile tissue to regain its pristine state.[20, 32]

1. Division of the pudendal nerves has not been satisfactory and has no relevancy to the important pathological changes which maintain the priapism.[3]

2. Division of the ischiocavernous muscles. The rationale of this method is based on the experience that shortening or imbrication of these muscles may produce successful erections in some cases of sexual impotency by the

compressive action of these muscles on the efferent cavernosal vessels.[28] This cannot affect the thrombosis in the cavernosal spaces.[1, 3, 20, 29]

3. Ligation of the dorsal arteries of the penis, the principle being that it halts the terminal flow of arterial blood. This cannot affect sinusoidal engorgement of the corpora, but could produce vascular insult to the penis[1] since it interrupts the distal artery directly.

4. Rectal diathermy. No logical basis for this treatment can be found.

5. Incision, excision or aspiration of localized areas of thrombotic induration in the corpora or perineum.[1, 43]

6. Radical amputation of the penis. This operation is the treatment of choice in primary malignant disease of the genital area which is extirpatable.

7. Incision of corpora cavernosa with manipulation and active drainage or passive drainage with irrigation.[28]

8. Percutaneous aspiration or evacuation of corpora cavernosa.

## EIGHT CASES OF PRIAPISM

CASE I (*Idiopathic Priapism*). F.I. (09336), a 54 year old male hospital attenddant, was admitted to Wadsworth Veterans Administration Hospital on April 2, 1963 complaining of painful erection of 3 days' duration. Erection was unexpected and sudden. There was a previous history of priapism 3 years earlier treated by cavernosal aspiration on the third day. Results were good and the patient maintained sexual potency following that episode. Physical findings were limited to the entire penis, which was erect, firm and pulsating. Laboratory studies were normal except for slightly elevated white blood count.

On the day of admission, after induction of spinal analgesia, each corpus cavernosum was aspirated using a 13-gauge needle, removing 100 cc. of dark blood from the right and 20 cc. from the left corpus. The corpora were irrigated with heparin in such a way as to distend and then evacuate each corpus. The penis promptly became flaccid. A pressure dressing was applied after inserting a urethral catheter. The pressure dressing was removed on the second postoperative day and the penis remained flaccid. The patient was seen by a psychologist who found him uncooperative. This priapism appeared to be an active erection. Toward the end of aspiration of the corpora bright red blood had been obtained.

This patient was seen 2 weeks after hospital discharge. He stated he had not experienced further erections.

CASE II (*Psychic Stimuli*). M.W. (61–1233), a 12 year old boy, was admitted to the Kansas University Medical Center on August 21, 1961, on the complaint of his mother that his penis seemed to be "always erect." She said she had never "caught him playing with himself" but he had been seen doing so by the neighbors. His family consisted of an adoptive mother, age 47, who had a hysterectomy because of adhesions, and, an adoptive father, age 51, who was quite concerned about the child's problem. The mother described the child as obedient and happy; however, since the onset of priapism, she had noticed that he had become more distant and withdrawn.

Physical examination revealed a well developed, thin, tall boy who was friendly and rather calm. Significant physical findings were limited to the genitalia and

consisted of a turgid, semi-erect and uncircumcised penis and some pubic hair. There were no pathological reflexes, no incoordination or other abnormal neurological signs. Laboratory findings and x-rays were normal. Urologic consultation confirmed these findings. No erection was present while asleep. Daily examination disclosed moderate erection of the penis, suggesting chronic masturbation.

The patient was dismissed with the following recommendations: Keep the penis in a downward position with an athletic supporter; encourage participation in normal activities; instruction in sexual matters by his father; privacy and regard for his developing maleness; emotional support and discussion of genito-sexual problems as objectively as possible.

*Comment.* Since this patient was never observed to have a complete erection, it might be conjectured that the erectile mechanism had already been damaged by long-standing priapism. On the other hand, the masturbatory or psychic stimuli active in this case may have been inadequate to produce a complete or sustained erection, therefore sedation (or sleep) or psychotherapy could prevent such a borderline case from developing into complete priapism.

CASE III (*Inflammatory Condition*). C.R. (04990), a 52 year old male dishwasher, was admitted to the Wadsworth Veterans Administration Hospital on September 9, 1960 complaining of painful penile erection of 7 days' duration. Erection began suddenly while he was washing dishes, and pain radiated into the perineum. During the past several weeks there had been dribbling of urine.

The patient's temperature on admission was 99.8° F., pulse 80, blood pressure 118/68. Examination disclosed an erect penis which was tender to touch but somewhat spongy throughout on palpation. There were no skin changes in the genitals. Twenty-four hours after admission inflammatory changes were seen in the scrotum and perineum and there was some induration at the base of the penis, suggesting suppuration. The temperature became elevated to 104.6° F. shortly after admission. Forty-eight hours after admission there was progressing cellulitis in the genital area, with crepitation at the base of the penis and edema of the scrotum.

On September 11, 1960 a suprapubic cystotomy was performed. The superficial fascia was edematous. After completion of the cystotomy, multiple incisions were made down to Colles' fascia, to the right inguinoscrotal area and to the base of the penis. Several other incisions were made along the penis down to Buck's fascia, evacuating pus and sanguineous material. The patient was then placed in lithotomy position and the urethra calibrated. A stricture was found in the bulbous urethra; this was dilated and a catheter inserted. An incision was then made through the scrotal septum and midperineum down to the bulbous urethra. An abscess was drained in the area and the drainage tract from this area was made to communicate with the inguinoscrotal incisions previously placed. The penis remained erect, however, and consideration was given to incising or aspirating the corpora cavernosa at this time, but this was deferred. The temperature declined immediately following surgery to 100° but remained remittent between 98.6° and 101° for 5 days. Urine culture was sterile. Pus from the perineal abscess was positive for hemolytic staphylococcus sensitive to all routine drugs.

After four days of observation of the patient the penis remained somewhat erect and its base and the right corpus became shiny, reddened and somewhat fluctuant. It was suspected that cavernositis was present. On September 15, 1960 the right cavernosal body was incised, evacuating foul-smelling, grumous, bloody material. The cavernosal body was largely destroyed and necrotic. The penis immediately became softer and more flaccid.

The postoperative course thereafter was uneventful. The wounds were periodically irrigated and by September 20, 1960 the drains were advanced and gradually removed until on October1 all drains were removed. The necrotic corpus cavernosum on the right side healed by granulation and scarring. The defect in the urethra closed slowly. The patient has been treated regularly since that time for urethral stricture. The penis is fibrotic. A urethrogram on October 24, 1960 disclosed an intact urethra with evidence of chronic inflammatory change but good caliber.

CASE IV (*Traumatic and/or Inflammatory*). C.B. (012681), a 41 year old man, was admitted to Wadsworth Veterans Administration Hospital on Feburary 14, 1964 complaining of genital pain and persistent erection. He was confused, and interrogation of his wife indicated that he had been having voiding difficulty for several months. She also stated he was losing weight, his appetite was poor and he was becoming weaker and unable to work. One day before admission he reported to a local physician who unsuccessfully attempted to introduce a urethral instrument. Following the instrumentation urethral bleeding developed. Shortly thereafter, he developed priapism which persisted to the time of admission.

At admission there was no clear-cut history of chills, fever, kidney or bladder pain. After urethral instrumentation and bleeding the patient was unable to void. Physical examination revealed a tense, anxious male complaining of penile pain. The penis was firm and tender throughout and markedly erect. The bladder did not seem to be distended. The white blood count was 45,550 with 86 per cent neutrophils. Hemoglobin was 10.8; hematocrit, 30 volume packed cells. No urinalysis was obtained because of the inability of the patient to void.

On the day of admission the corpora were aspirated under spinal anesthesia with a 13-gauge needle with decrease in the size of the penis and some deturgescence. At the time of aspiration, the urethra was instrumented in order to introduce a urethral catheter. When the catheter entered the bladder a large amount of purulent material mixed with urine was obtained. The catheter was left indwelling and a compression dressing placed over the penis. Culture of material obtained from the bladder revealed microaerophilic streptococcus sensitive to routine drugs. The blood smears, examined by the hematologist 36 hours later, were interpreted as leukemoid reaction. On the second hospital day the patient's temperature began to rise and his general condition appeared to be deteriorating. Blood urea nitrogen was found to be 148.5 mg./100 ml. and serum bicarbonate 9.3 mEq./L. The penis became increasingly tender with edema and a mass on the right side of the perineum in the subpubic area extending up toward the right inguinal region.

On February 17, 1964, under spinal analgesia, incision in the right genitocrural and perineal areas disclosed a large perineal and periurethral abscess extending from the bulbous urethra posterior to the prostate and bladder and upward toward the inguinal area on the right side. There was no evidence of a defect in the urethra. Pus obtained at incision and drainage was reported as due to microaerophilic streptococcus sensitive to routine drugs.

Several drains were placed deep in the abscess cavity with counter drainage in the right inguinal region and the base of the penis. The penile erection gradually subsided during the following week. Blood urea nitrogen rose from 148 mg. to 219 mg./100 ml. by February 20, 1964. On the following day diuresis commenced and by March 1 the blood urea level was 15.5 mg./100 ml. The wound drains were removed on March 2 and the area healed by granulation. A urethrogram on March 3 disclosed no evidence of narrowing or irregularity, but the prostatic urethra was slightly elongated. The patient has been voiding satisfactorily. He was examined on March 31, 1964 at which time induration at the base of the penis was still present but all wounds were firmly healed. The urine culture was negative. He had had no erection since discharge from the hospital.

*Comment.* It is possible that this patient had instrumental rupture of the urethra with extravasation or remotely a perirectal abscess which burrowed forward into the urogenital area.

CASE V (*Sicklemia*). P.W. (59–11952), a 29 year old male Negro, was admitted to the Kansas University Medical Center on August 11, 1959 (his first admission), complaining of painful erection of 19 days' duration. He had been well until July 23, when he awakened with a painful persistent erection. There was no history of joint pain, and no family history of sickle cell anemia. He also complained of left chest pain. Past medical history, family history and review of systems were noncontributory to the present episode.

Upon physical examination the man appeared to be well developed and well nourished, and seemingly not in acute distress. His blood pressure was 100/90, temperature 98.6° F., pulse 84 and respirations 20. The examination was negative except for the abdomen. There was generalized abdominal pain and the spleen was palpable 1 fingerbreadth below the left costal margin. The patient had bicorporal penile erection. Urinalysis was normal. Blood findings were: white cells 24,000 with normal differential count; no anemia; platelets 884,000; sickle cell preparation positive for sickling; acid phosphatase 0.7 unit; alkaline phosphatase 1.2 units; serum bilirubin total 2.5 mg./100 ml.; Coombs test negative. Bone marrow biopsy revealed a marrow of erythroid hyperplasia. Chest x-ray showed consolidation of the left lower lung field consistent with pneumonia or pulmonary infarction. The patient was given anticoagulants, the prothrombin time being maintained between 15 and 25 per cent of normal. After treatment for about 2 weeks, his penis began to get smaller and more flaccid. At the time of his discharge from the hosiptal it was approximately half the size it was on admission, and in a semi-erect state. He was well regulated on 5 mg. of Coumadin by mouth daily, which resulted in a prothrombin time of 18 to 19 per cent of normal. The patient was to be followed by his family physician at home while receiving anticoagulants as an outpatient and followed in the clinic until his erection completely subsided. The pulmonary changes gradually cleared.

Final Diagnoses: sicklemia; priapism due to sicklemia; infarction of lung due to sicklemia.

CASE VI (*Leukemia*). J.L.S. (59–2391), a 49 year old caucasoid male, was admitted to Kansas University Medical Center on January 12, 1959. Penile erection had had its onset on January 10, and had persisted until his admission. Voiding difficulty had begun 12 hours after the onset of erection. He stated that during the 2 weeks prior to admission he experienced penile erections of spontaneous onset which had persisted one to two hours, then subsided completely. He also complained of a 30-pound weight loss during the previous 3 months accompanied by fatigability and occasional nausea with vomiting.

Upon physical examination, the patient was a well nourished, well developed, ambulatory male who appeared to be chronically ill. Temperature, pulse and blood pressure were normal. The abdomen was somewhat protuberant with an enlarged liver and spleen. The genital area disclosed priapism with turgescence of both corpora cavernosa. The glans was soft. There were no significant changes in the scrotal contents, perineum or prostate.

The laboratory findings were: urinalysis normal; hemoglobin 11 grams; white blood cells 185,000 per cu. mm. with 61 per cent polymorphonuclear leukocytes, 7 per cent metamyelocytes, 23 per cent myelocytes, 4 per cent lymphocytes, 1 per cent eosinophils, 4 per cent basophils; 769,000 platelets per cu. mm. Blood chemistries were normal.

It was evident from the physical and laboratory findings that this patient had

priapism secondary to myelocytic leukemia. He left the hospital against medical advice and further examination and treatment were not possible.

CASE VII (*Pelvic Thrombophlebitis*). L.G. (63–7126), a 32 year old man, was admitted to St. Luke's Hospital on April 22, 1963 with bizarre symptoms suggestive of appendicitis, namely pain in the right lower chest and epigastrium finally localizing in the right costovertebral angle and the right lower quadrant. At laparotomy on April 23, 1963, no pathological process was found. The appendix was removed and reported "appendix showing no active inflammation." Biopsies of skeletal muscle and liver were normal. The patient was dismissed on May 5, 1963, asymptomatic.

The patient was readmitted 11 days later with pain in the left leg and findings consistent with left iliofemoral thrombophlebitis: marked tenderness over the left femoral ring, along the saphenous vein and in the left calf; a positive Homan's sign in the left leg, and edema of the left foot. He was placed on anticoagulants. Two days after hospitalization he developed tightness in the chest, chest pain and pain in the right side aggravated by deep breathing, suggestive of pulmonary emboli. Then on May 22, 1963, when coughing, he had sudden pain in the left testicle and an immediate pathological erection typical of priapism.

On May 20, 1963, the prothrombin time had been 39 per cent of normal, on May 21, 32 per cent of normal, and on May 22, the day of the priapism, it was 24 per cent of normal. It was maintained at this level but the penile response to this conservative management was poor. By May 24 the glans penis was very hard and cyanotic. Spinal and thiopental (Pentothal) anesthesia produced no improvement. Multiple puncture wounds were made in the glans penis and heparin solution was injected into the corpora. A pressure dressing was applied to the penis and a No. 16 Foley catheter left indwelling. The subsequent course was favorable with gradual penile softening. The urethral catheter was removed on May 31. The foreskin became necrotic and debridement was done on June 4. Convalescence from that time was satisfactory and the patient was dismissed ambulatory and voiding well on June 22, 1963. He reported having satisfactory erections and sexual intercourse at a follow-up visit on August 9, 1963.

CASE VIII (*Idiopathic or Psychophysiologic*). R.K. (64–5031), a 66 year old bachelor, was admitted to St. Luke's Hospital on April 10, 1964, with a history of awakening at 3:00 A.M. with an erection and being able to void only a small amount at that time. He had been awakened for many months with painful erections but these would subside after voiding. He had been taking a proprietary acetylsalicylic acid–phenacetin medication, at least 3 tablets per day, for the past 6 months for headaches. He was sexually active as recently as 1 week prior to present illness. Physical examination was normal, except for a pathological erection involving the corpora cavernosa. Urinalysis revealed many pus clumps.

A regimen of heparin and Dicumarol was inaugurated, with satisfactory anticoagulant effect but no improvement in the erection. On April 12, 1963, spinal anesthesia produced no penile softening. On the following day spinal anesthesia was given and multiple 1-cm. incisions were made into each corpus with extrusion of old grumous blood and immediate softening of the penis. Within 12 hours, however, the erection had recurred with its original vigor, therefore, on April 16, under spinal anesthesia, three loops of No. 8 fenestrated plastic tubing were inserted "through and through" in each corpus with prompt collapse of the priapism. Drainage on the left side of the penis became purulent. The patient became quite depressed. Psychiatric consultation was obtained with a diagnosis of "agitated depression."

The patient was dismissed on May 11, 1964 and followed as an outpatient, his only treatment during this period being tetracycline and Empirin Compound. Purulent drainage from the left corpus improved, but pyuria continued. He was treated with chloramphenicol (Chloromycetin) with change from purulent to watery

penile drainage and microscopically negative urine. The penis gradually became fibrosed, attaining the consistency of hemp rope; not much hope is held for any further erections.

## DISCUSSION

While some intriguing forms of treatment for priapism, such as the use of hypotensive anesthesia, proximal interruption of the internal pudendal artery, anastomosis of corpus to saphenous vein, and the use of anticoagulants and lytic enzymes, have been successful in reported cases, there are limitations to the application of these forms of therapy. The presence of severe hypertension or arteriosclerosis, cases presenting for treatment after a prolonged period of erection, poor-risk cases, and the presence of hematologic disease may contraindicate or render ineffective one or more of these forms of treatment. These vaso-interruptive, hypotensive and anticoagulant treatments nevertheless are logical approaches in selected cases to prevent augmentation of turgescence or to aid in removing the altered blood trapped within the sinus spaces of the corpora cavernosa in the early stages. Most investigators, however, report that these methods have been successful only when combined with aspiration. *The sequestered blood must be evacuated since it becomes an irritant.* When the treatment is delayed and cavernosal damage is advanced, the only possibility of relief, or residual function, depends upon removal of this trapped blood.

There is apparently a transitional phase during which the sinoendothelial structures have not been too badly damaged so that the use of lytic enzymes or anticoagulants will permit outflow of the entrapped blood when this blood is "thinned out."[16, 32, 38] The return of coital effectiveness depends upon age of patient and length of time elapsed since the onset of priapism. The use of incisions into the corpora cavernosa may occasionally result in localized fibrosis of Buck's fascia or the tunica albuginea with a "squint" of the subsequently erect penis toward the side where the fibrosis has occurred.

In reviewing cases in which aspiration was used, the size of the needle has varied from 8 gauge to 17 gauge, and the points of aspiration have been placed from the base of the corpora to the coronal area of the penis. The advantages of percutaneous aspiration and evacuation of the corpora are: (1) it is a relatively minor procedure; (2) it does not require major anesthesia; (3) it requires only minimum equipment and assistance; (4) there are no major alterations in vital systems; (5) it can be repeated without major preparations; (6) it promptly relieves acute penile pain, anxiety, and voiding difficulty; (7) there is no need to delay treatment for baseline studies except those needed to rule out hematological or neurological disease; (8) impotency is not absolute, in many cases it is partial, and in some cases complete restoration of function occurs; (9) it may be used to complement or supplement other procedures.

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# Hydroceles and Varicoceles

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A hydrocele or varicocele is not an uncommon occurrence in the scrotal compartment of the adult male. Their occurrence is less frequent in the young or infant male. A varicocele is secondary to an altered venous physiology of the blood supply of the testicle. A hydrocele is usually secondary to an abnormality in the lymphatic drainage of the testicle. These two entities will be discussed as separate subjects.

## VARICOCELES

In 1550 Ambroise Paré defined a varicocele as a compact group of vessels quite filled with melancholic blood.[30] During the ensuing 400 years, various operative procedures and therapeutic methods have appeared in the literature. The concept that the condition is self-limiting, the symptoms trivial, and the complaints are unrelieved by operation have become commonplace. There is also prevalent in American literature the suggestion that a hypochondriacal state may exist if the patient complains of the discomfort of a varicocele.

An Armed Forces study places the incidence of varicocele at 16.5 per cent.[2] The first symptoms may occur between the ages of 15 and 30. Of this group 98 per cent are left-sided, 2 per cent may occur bilaterally. There are no known cases in the literature of a unilateral right varicocele of an idiopathic type. A unilateral right varicocele or a sudden acute varicocele of the left side may denote serious, systemic, retroperitoneal disease such as carcinoma of the kidney or retroperitoneal tumor.[27, 28] Approximately 33 per cent of patients with varicocele are actively symptomatic.[2, 9, 19, 24, 26, 27, 30]

### Varicocele Syndrome

Venous Physiology. Consideration of the altered venous physiology involved allows one to predict the symptoms of a varicocele. Hanley and

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Harrison[8, 9] have worked out the anatomical and physiological considerations for varicoceles and have found that, when the weight of the testis is placed upon the cord structures rather than the dartos and cremasteric muscle, there is a dull, dragging type of pain extending up into the groin. The normal testicle is supported principally by the dartos muscle which bears the whole weight of the testis under normal conditions. In emergency situations the cremasteric muscle can pull the testicle up to the external inguinal ring for a brief period, but the cremasteric muscle is not designed as a permanent weight bearer of the testicle. A large varicocele or hydrocele increases the scrotal temperature with concomitant elongation of the scrotal wall allowing the full weight of the testis to be borne by the cord structures.

CLINICAL PICTURE. Olson and Stone[19] have succinctly described the clinical picture and state that the patient notes gradually increasing scrotal enlargement and pendulousness during the course of a day of erect posture. The process is hastened by exertion with the resultant sense of heaviness of the scrotum, followed by a dull, dragging, aching, constant, pulling pain felt in both the scrotum and the groin. This pain disappears slowly with rest in the supine position and is generally absent on arising in the morning. The discomfort has been described as of the traction type caused by pulling or weightbearing on the spermatic cord structures. Other symptoms should be viewed with a suspicion that they are secondary to other disease processes. A sharp or stabbing pain suggests orchitis, epididymitis, orchialgia or hernia. Occasionally a venous thrombosis secondary to trauma may result in sharp pain in the scrotum for a short time.

**Depression of Spermatogenesis**

The most distressing disturbance associated with varicoceles is subfertility. The first noticeable effect is on the motility of the sperm, the second, on the total number of sperm present. This factor has been determined to increase with age with a marked increase in subfertility in the 30 to 40 age group[24] (Fig. 1).

PHYSIOLOGY. Scott and Young[25] have discussed three ways in which varicocele may produce a deleterious effect on human spermatogenesis. (1) Varicoceles may destroy the germinal epithelium of the testicles, in the same manner that varicose veins of the leg may lead to local skin destruction. (2) The testicle is held in position by the weight of the varicocele, thus preventing the efficient operation of the normal physiological cooling mechanism. (3) The large volume of circulating blood acts as a radiator surrounding the testicle. Hanley[8] by the use of thermocouples found that varicoceles raise the intrascrotal temperature by as much as 2.8° C. A left varicocele was found to increase similarly the temperature of the right scrotal compartment. Subsequent testicular biopsies revealed bilateral histological changes. This progressive bilateral deterioration can be altered and fertility returned to normal by varicocele ligation.

SUBFERTILITY. Subfertility refers to the relative number of sperm,

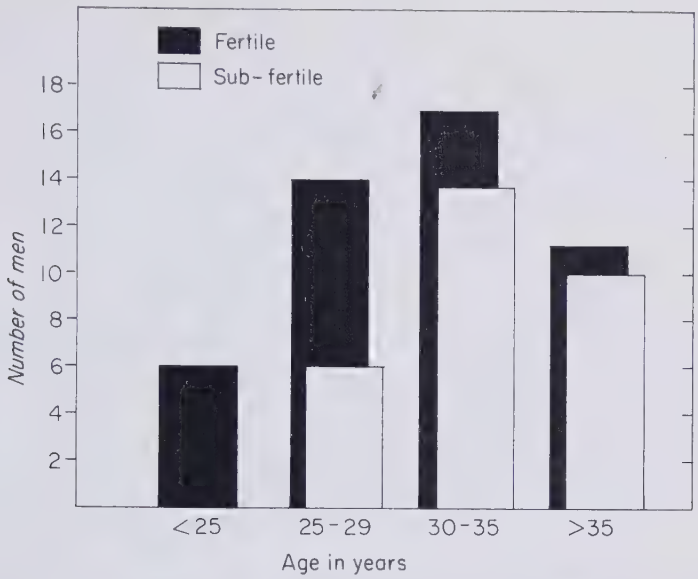


Figure 1. A diagrammatic representation of adult males with varicoceles divided into fertile and subfertile groups. Note the increased instance of subfertility as the age of the patient increases. (From Russell, J. K., Lancet *2:* 222, 1957.)

since there is a wide variation in the normal count of 40 million to 160 million sperm per cubic centimeter. A varicocele could therefore suppress spermatogenesis 50 per cent and leave the patient fertile in one case and subfertile in another. There are numerous references, particularly in the English literature, pertinent to this subject.[8, 9, 19, 24, 25, 30, 31]

## Anatomy of the Venous Circulation of the Testicle

DEEP SYSTEM. The chief drainage of the testis is by way of the internal spermatic vein, which is typically a single vessel as it enters the abdomen, forming in the lower part of the spermatic cord the dense pampiniform plexus (Fig. 2). The pampiniform plexus, on the basis of relationship to the vas deferens, is divided into three groups of vessels comprising the deep system.[11, 13] The anterior group surrounds the artery, the posterior one passes upward from the epididymis, and the middle group consists of the veins closest to the vas. A varicocele may be located in any one of the three groups. In the majority of cases, the spermatic vein (anterior group) is the only one involved; however, the cremasteric (posterior group) and rarely the deferential vein (middle group) have been indicted.[8, 9] The venous drainage of the scrotal contents can be compared to that of the extremities.

SUPERFICIAL SYSTEM. The superficial system or secondary drainage system consists of the superficial and deep inferior epigastric veins, the superficial internal circumflex and the scrotal tributaries of the superficial and deep external and internal pudendal veins (Fig. 2). The anastomosis

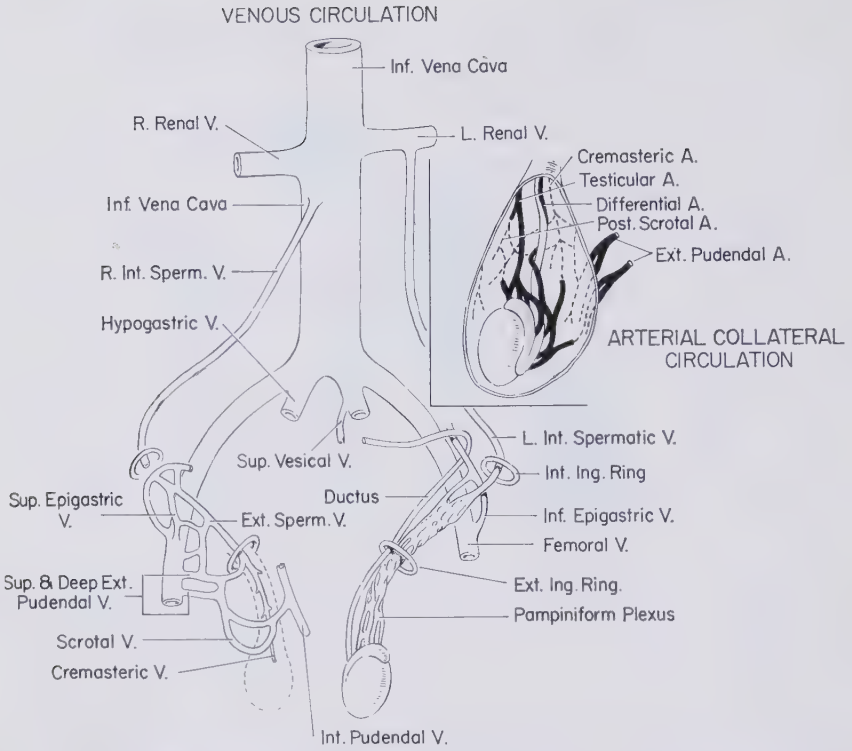


Figure 2. The anatomy of the deep and superficial venous circulation of the testicle. The arterial collateral circulation showing the anastomosis.

of the veins occurs distal to the external ring, therefore a surgical procedure, when in the confines of the inguinal canal or above the internal inguinal ring, would obviate any interruption of the collateral venous return.

The great preponderance of varicoceles on the left has been explained by the anatomical consequence of the entrance of the left internal spermatic vein into the renal vein at a right angle. The hemodynamics of this is not perfectly understood.

## Anatomy of the Arterial Circulation

The testicle is fortunate in having multiple sources of collateral arterial supply and is not dependent entirely upon the testicular or deferential arteries. There are anastomoses not only between the deferential and testicular arteries, but also between these arteries and the arteries which supply the scrotal sac. The artery of the ductus deferens anastomose effectively with the testicular artery in all cases. In approximately two-thirds of the cases, the cremasteric artery also has a functional anastomosis which connects with the other two arteries (Fig. 2). In only one-third of the cases is the sum of the diameter of the cremasteric artery and the artery of the ductus at least equal to that of the testicular artery.[9] Neuhof and Mencher[18] found

that, after complete severance of the spermatic cord, the collateral blood supply was sufficient to prevent gangrene. In spite of collateral circulation, however, there was gross evidence of atrophy in about 80 per cent of the patients. Although it was apparently mild in two-thirds of these, it was obvious in about one-third. The collateral arterial circulation is sufficient in probably one-third of the cases. These conclusions mitigate against the use of any procedure which contemplates severance of both the testicular artery and the spermatic vein.[21]

## Operative Indications and Techniques

There are only two indications for varicocelectomy; namely, pain consistent with the typical variocele syndrome or serious depression of spermatogenesis.[8] Optimum results have been obtained with an incision in the abdominal area, either over the inguinal canal or above the internal inguinal ring.[12, 13, 14, 32] Ligation of the internal spermatic vein as it either enters the internal inguinal ring or as it leaves it superiorly is preferable (Fig. 3). The inguinal canal should be fully explored since, in 20 to 25 per cent of these cases, there is a coexistent inguinal hernia present.

INGUINAL EXPOSURE. A diagonal skin incision is made from the area of the external inguinal ring to an area approximately 1¼ inches above the lateral point of Poupart's ligament. The external fascia is split just above the external ring and is enlarged with scissors for a distance of several inches. The spermatic cord is completely freed to the level of the internal ring. A

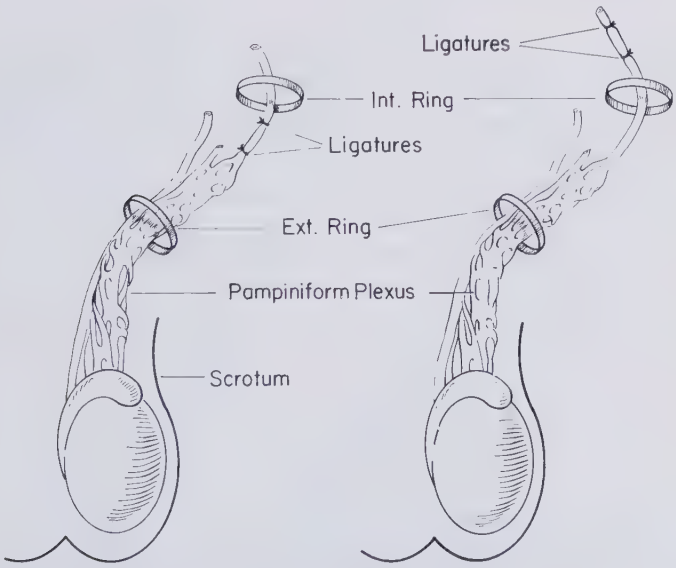


Figure 3. Optimum results in varicocelectomy have been obtained with ligature and severance of the spermatic vein either at the internal ring or superior to the internal ring.

small branch of the iliohypogastric nerve is reflected upward and laterally to prevent injury. The cord structures are then drawn upward with a Penrose drain to expose the floor of the inguinal canal. The cremasteric fascia is opened longitudinally and the internal spermatic vein is isolated preferably at or near its entrance through the internal inguinal ring. Approximately 40 per cent of these cases may have two veins in this area.[19] A 1-inch segment of the vein is isolated and severed between ligatures. The proximal end is allowed to retract retroperitoneally. Care is taken to avoid injury to the vas deferens or the testicular or deferential arteries. If a hernia is present, it is then repaired in the conventional manner. The cremasteric fascia is closed in the direction of the wound with 00 chromic catgut suture. The external oblique fascia is approximated in a similar manner and the skin and subcutaneous fascia are approximated using black silk.

No effort is made to close the cremasteric muscle transversely or to tie the severed ends of the varicose vessels together in order to shorten the cord since the primary supporting structure is the dartos muscle which will soon react by shortening the scrotum. A scrotal support is worn for four or five days since there is some edema following this procedure.

RETROPERITONEAL EXPOSURE. A second method of approach to this problem is a short incision above the internal inguinal ring with retroperitoneal exposure of the internal spermatic vein and the spermatic cord (Fig. 3). The internal spermatic vein is isolated and approximately 1 inch is removed between clamps, the severed ends being doubly ligated and allowed to retract retroperitoneally.

### Conclusion

The concept of a deep and superficial venous circulation of the testicle similar to that found in the extremities is presented. Varicoceles produce a deleterious effect on human spermatogenesis due to vascular and temperature changes. Fertility can be returned to normal by varicocele ligation. The physiological mechanism of the typical varicocele syndrome is presented and a suggestion is made that the results following varicocelectomy are most gratifying in those cases which conform to the typical varicocele pattern. Ligation of the internal spermatic vein is carried out retroperitoneally or at the deep inguinal ring. Pessimism concerning varicocelectomy is no longer justified using high ligation.

## HYDROCÈLES

The testicle embryologically is a retroperitoneal organ and on its descent into the scrotum carries with it a portion of the peritoneum. The processus vaginalis connects the upper end of the testis and the internal inguinal ring and is normally obliterated. The tunica vaginalis covers the front and most of the sides of the testis and part of the closely attached

epididymis, forming a closed sac. A portion of the sac which is not in contact with the testicle is known as the parietal layer. The sac of the tunica vaginalis normally contains a small amount of serous fluid and an increase in the amount of fluid present is known as a hydrocele. Because of the variations in the tunica vaginalis and in the fate of its original connection to the general peritoneum and internal ring, hydroceles may take several anatomical forms.[11] The lymphatics of the tunica vaginalis have no drainage into the inguinal nodes; rather, they extend upward to the periaortic nodes in the area of the renal arteries.[20] Rinker and Allen[23] have rather beautifully shown that hydroceles have a defective lymphatic drainage with inadequate reabsorption of serous fluid within the sac of the tunica vaginalis. The pathogenesis of the hydrocele is based on an imbalance between the secretion and reabsorption of fluid within a closed sac.[20]

## Types of Hydroceles

The congenital hydrocele with or without hernia is secondary to failure of closure of the processus vaginalis with consequential communication between the tunica vaginalis and the peritoneal cavity (Fig. 4, *B, E*). Infantile hydroceles have the same etiological background with the exception that the finger-like pannicular process has failed to close and extends upward to various levels in the scrotum or inguinal canal but does not communi-

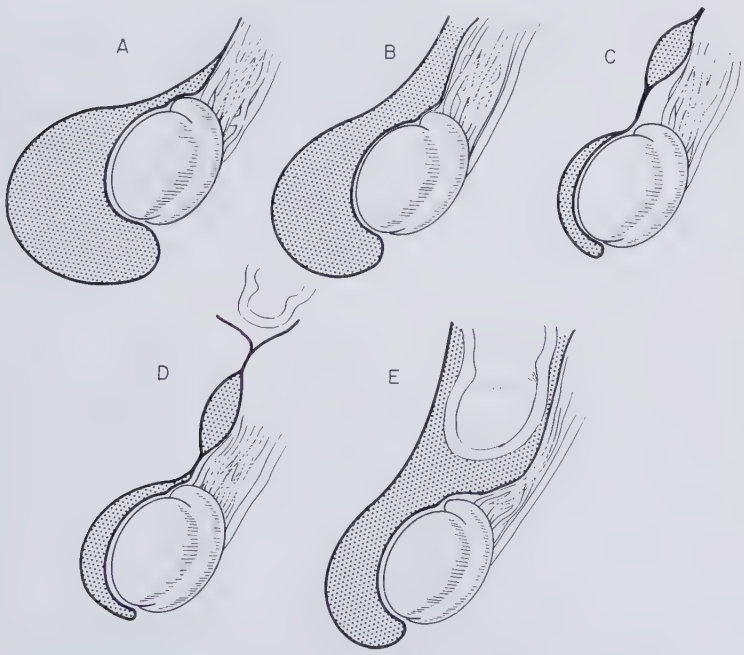


Figure 4. Types of hydrocele. *A*, Simple hydrocele; *B*, congenital hydrocele; *C*, hydrocele of the cord; *D*, hydrocele of the cord with a hernia; *E*, hydrocele with a hernia.

cate with the peritoneal cavity. A simple hydrocele is an accumulation of fluid within the sac of the tunica vaginalis (Fig. 4, *A*). A hydrocele of the cord[17] occurs as a collection of fluid within a portion of the processus vaginalis, which is not obliterated and does not communicate with the tunica vaginalis or the peritoneal cavity (Fig. 4, *C*). There is a rare type of abdominal scrotal hydrocele which extends upward from the scrotum into the retroperitoneal area.[3] Hydroceles have been classified etiologically as primary or secondary types. The primary hydrocele has its basis in unknown causes. The secondary hydrocele is a complication of such diseases as orchitis or epididymitis, or it may result from generalized systemic disease processes.

**Diagnosis**

The diagnosis of a hydrocele is based primarily on palpation of a soft, doughy mass in the scrotum and on the passage of light through this mass on transillumination. In infants the rectal examination[6] may be a useful maneuver to aid in differentiating an incarcerated inguinal hernia from a hydrocele (Fig. 5). In adults the penis appears to be shortened as the hydrocele enlarges and extends upward in the scrotum as opposed to carcinoma of the testicle, which conversely makes the penis appear longer. The main diagnostic factors of importance are the differentiation of a hydrocele from disease or tumor of the testicle, epididymis, cord or a hernia. Some hydroceles fail to pass light on transillumination because of their chronicity with the resultant thickening of the tunica vaginalis. If there is any doubt as to the diagnosis, the scrotal mass should be aspirated and the contents of the scrotum palpated following emptying of the tunica vaginalis. This is quite important, particularly when a hernia or a possible carcinoma of the testicle coexist with a hydrocele. In any intrascrotal operation a prophylactic hydrocelectomy should be done since the incidence of hydrocele is high following a scrotal procedure.[2]

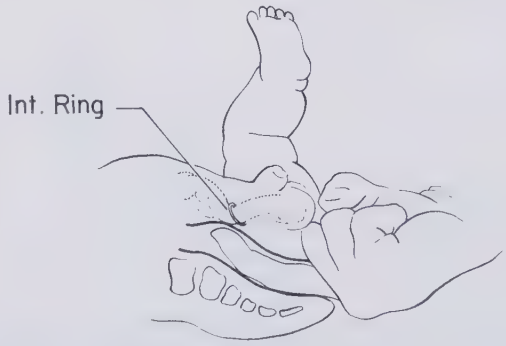


Figure 5. Palpation of internal inguinal ring through the rectal wall in an infant to differentiate an incarcerated inguinal hernia from a hydrocele.

## Treatment

The treatment of a hydrocele is based on (1) periodic removal of the hydrocele fluid by aspiration; (2) destruction or removal of the secreting surface of the tunica vaginalis; (3) allowing the lymphatic fluid to drain into the adventitia with reabsorption by normal lymphatic channels.[10, 15, 20, 22, 23]

TREATMENT IN INFANTS AND CHILDREN. The choice of treatment of a hydrocele is determined by the age of the patient. Hydroceles of the tunica vaginalis in children under one year of age seldom require operation as the majority regress spontaneously. The main indication for surgery in this group is the presence of an associated hernia. After the age of two, an operation is advisable, particularly when the hydrocele has been present for a long time and varies in size.[2, 22] Because of the possible persistent patency of the processus vaginalis and because of the possibility of a concomitant hernia, the inguinal approach is used. The external oblique aponeurosis is split and the cremasteric muscle is separated to expose the cord as far as the internal ring. The testicle with the tunica vaginalis is drawn into the wound and 2 cc. of methylene blue dye is injected into the sac and the hydrocele is massaged gently. The resulting bluish discoloration of a patent processus vaginalis allows it to be easily detected, isolated and severed. A portion of the anterior wall of the tunica vaginalis is excised.[22] A hernia found at the time of surgery is treated in the conventional manner.[4, 5, 6]

TREATMENT IN THE ADULT MALE. The adult male who has an asymptomatic, small, nonprogressive hydrocele may require no treatment. In patients of older age with a symptomatic, large hydrocele who are poor surgical candidates, repeated aspirations will not be curative, but will give relief of these symptoms. Injection of sclerosing material after aspiration has been advocated and used reportedly with success. Ozdilek[20] has presented a simple operative technique which consists of creating a fenestrating window in the hydrocele sac and allowing the fluid to drain into the adventitia. Injection therapy of complicated or secondary hydroceles is contraindicated.[2]

The treatment of a hydrocele in an adult patient requiring surgery has revolved around two principal operations. In the Andrew bottleneck operation the scrotum or inguinal area is entered and the hydrocele exposed and dissected free (Fig. 6). The sac is then opened and drained and the cut edges are everted behind the cord and sutured in place. This allows the everted, secreting tunica vaginalis to drain into the adventitia of the scrotum where it is collected by the normal lymphatics. This operation is particularly applicable in simple hydroceles. In large hydroceles which have a thickened wall, a Winklemann procedure is performed through a scrotal or inguinal incision (Fig. 6). The entire hydrocele sac is removed to within ¼ inch of the reflection of the tunica vaginalis from the testis and epididymis. The

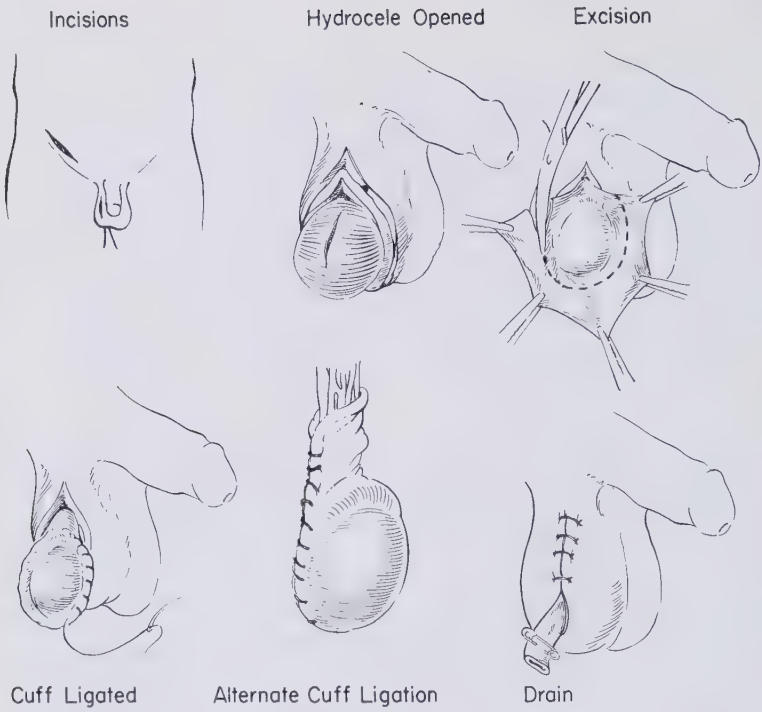


Figure 6. Removal of the hydrocele sac close to the epididymis and testicle with ligation of the cuff. Eversion of the hydrocele sac behind the cord structures with approximation of the cut surfaces by an alternate cuff ligation.

severed edges of the sac are then carefully sutured in order to prevent hemorrhage. A modification of this procedure is the Jaboulay method of excising most of the sac and everting the cut edges and suturing them behind the epididymis. A drain is left in place for 24 hours following surgery.

The treatment of a secondary hydrocele is conservative and directed mainly toward the underlying disease, which may be orchitis or epididymitis. Aspiration is used only for comfort in case of marked distention of the hydrocele sac.

## Summary

The anatomical and physiological considerations of hydroceles are discussed. A method of treatment of primary hydroceles in infants and children is presented which consists in ligation and excision of the processus vaginalis combined with the excision of part of the wall of the tunica vaginalis.[22] A herniorrhaphy is done at the time of operation if indicated. Several methods of surgical intervention in adult patients are considered. The implication is clear that as complete a removal of the sac of the hydrocele as possible is the most effective solution.

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# Hypnoanalgesia and Hypnoanesthesia in Urology

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Man has sought means for the relief of pain since his very beginning. When he discovered hypnosis he found an unusual but effective method.

The elimination of pain in the performance of urological manipulative and instrumental procedures can and has been accomplished with the use of hypnosis. The urologist sufficiently interested in obtaining the necessary training will find it most useful in this regard. The anesthesiologist can, in selected cases, use hypnosis for anesthesia in urological operations, both major and minor. The following general review of the subject is intended to interest not only these specialists but all fellow practitioners.

## Historical Sketch

Hypnosis is as old as civilization itself, and record of its use dates back 3500 years. The superstitious ancients, various religious leaders and prophets relieved pain and performed "cures" rather mysteriously with hypnosis in a manner little different from that used today. During the medieval era charlatans and sorcerers brought it into disrepute.

In 1773 Anton Mesmer introduced the hypnotic phenomenon to scientific medicine. Puysegar changed his "animal magnetism" theory to that of a "state of mind." Recamier and Dupotet, in Paris, were the first to use "mesmerism" as a sole anesthetic in surgery in 1821, 25 years prior to the advent of chemical anesthesia. Jules Cloquet used it in 1829 to perform a mastectomy. In 1837 Oudet, a French dentist, performed teeth extraction using "mesmerism." Three years later James Braid, an English surgeon, changed the term "mesmerism" to hypnosis. In 1840 Elliotsan championed its use in England against great opposition. About the same time James Esdaile, working in a prison hospital in India, reported 300 major surgical operations and several thousand minor ones using only hypnosis, with a greatly reduced mortality. In this country, about the same time, Albert

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Wheeler performed a polypectomy, Doane and Ackley each removed a tumor from the neck, and Dugan did a breast amputation using hypnosis.

After the introduction of ether anesthesia in 1846 the use of hypnoanesthesia began to wane. There was some resurgence during World Wars I and II but with no great general acceptance. In 1953 the British Medical Association officially endorsed the teaching of hypnosis in all of its medical schools. It was not until June 1958 that the House of Delegates of the American Medical Association endorsed the cautious use of hypnosis by the medical profession.

At the present time less than a dozen of this country's medical schools offer instruction in medical hypnosis but the list is slowly growing.

### Definition

What is hypnosis? In this regard the literature is very confusing and offers no universally accepted definition. Despite this difficulty, I would attempt to define hypnosis as a psychological phenomenon, resembling twilight sleep, involving a temporary dissociation between the conscious and subconscious parts of the mind, and depending upon an unexplainable interpersonal relationship between a subject and a hypnotist wherein the latter can, by various techniques, produce in the former a state of hypersuggestibility.

## THE NATURE OF HYPNOSIS

Before I discuss the indications, disadvantages and performance of hypnoanesthesia and hypnoanalgesia, it is of interest to discuss something of the nature of the hypnotic phenomenon. To begin with, who can be hypnotized? Almost anyone who does not deliberately reject hypnosis and who has no subconscious resistance to it can be hypnotized. Intelligence is not an important factor, although an ability for some degree of concentration and an understanding of directions are essential. An imaginative person and one who believes he can be hypnotized usually makes a better subject. Artists, actors, teachers, lawyers and most professionals in fields requiring imagination render a better response to hypnosis. The well-motivated person looks to hypnotherapy for help, even salvation, and, therefore, succumbs to it more readily. The person seeking relief from the pain of surgery and the fear of entering the unconscious anesthetic state needs no better motivation.

It has been said that the common soldier makes a better subject than his superior officer who gives rather than receives orders. Confidence in the hypnotist, who understands the patient's motivation, allows the patient to respond more easily. The operator's confidence in his own ability is also an important factor in obtaining a favorable result. There seems to be little difference in the hypnotic response of the sexes. Children old enough to

understand language can respond to hypnosis, i.e., from about the age of two years upward. As a rule, because of their willingness to try new experiences, induction is easy in children. The young adolescent, age 14, makes the most satisfactory subject. Some writers contend that aged subjects are less responsive, but urologists who deal extensively with older people find that the alert and cooperative older person, irrespective of age, can be hypnotized.

Who can and who should employ hypnosis? The ability to hypnotize does not require any special mysterious gift. Anyone of average intelligence can learn the fundamentals of the technique in a few hours. Short courses in the technique by professional as well as lay teachers are offered around the country, but these programs are not condoned by the Committee on Hypnosis of the American Medical Association. Although any physician can learn the art and science of hypnosis, it seems that those possessing the most empathy and showing patience, warmth and sympathetic understanding and those exuding confidence are the best performers and achieve the best results. Surgeons who fulfill these qualifications seem to make better hypnotists than do their nonsurgical colleagues.

What happens when one is hypnotized? Subjects have described various sensations. Some feel the same type of abandon or loss of inhibitory response experienced with alcoholic intoxication. Others describe a spinning or dizzy sensation, and still others, a floating or falling sensation. Most subjects report being comfortably relaxed with a feeling of heaviness all over, and all seem to manifest a willingness to please the hypnotist in following any reasonable suggestion. Thus the physician is in an advantageous role directing his patient toward his optimum good.

The patient, by his attitude, gives the impression that he is asleep. Actually, his sensitivities are sharpened, and he can almost feel the sincerity of his physician-hypnotist, or the lack of it. His state of hypnotic "sleep" is unlike real sleep in that his reflexes remain normal and his encephalogram fails to reveal the alpha waves of a true sleep.

## STAGES OF HYPNOSIS

Various stages or depths of the hypnotic state have been described. These stages and their approximate percentages of occurrence are listed below.

1. *Not hypnotizable at all* (10 per cent)
2. *Hypnoidal stage*—fluttering of the eyelids (10 per cent)
3. *Light stage*—limb catalepsy (40 per cent)
4. *Medium stage*—analgesia, hypnotic and posthypnotic (20 per cent)
5. *Deep state*—anesthesia for minor surgery (10 per cent)
6. *Somnambulistic stage*—anesthesia for major surgery (10 per cent)

The percentages listed vary with the ability of the hypnotist. They are

for stages obtained in relatively short treatment time. A deeper stage may be obtained by persistent effort over a longer period. One cannot anticipate the obtainable depth for any particular subject prior to induction. The stage will vary as much as will the ability of hypnotists. Some patients will not respond to one hypnotist but will to another. Some may submit lightly the first time and more deeply at each successive trial.

## INDICATIONS

What are some of the advantages in using hypnosis in surgery? There is no method or tranquilizer drug that can more effectively allay the fear of the operation or the anesthetic, or of the fear of dying, than the reassurance given to the subconscious mind in the hypnotic state, preoperatively. Hypnoanesthesia, used alone if possible, is actually the ideal anesthetic, because it frees the patient of the depressive toxic effects characteristic of the chemical anesthetics. It does this also with little change in the normal physiological processes. By its use the operative risk can be reduced in patients with cardiac, respiratory, kidney or liver disease. When hypnosis cannot be used alone, it is invaluable as an adjunct to chemoanesthesia, because it can reduce the amount of chemical anesthetic by as much as 50 to 75 per cent. Sensitivity or allergy to all chemoanesthetic agents is certainly an absolute indication for the use of hypnosis. To prevent neurogenic shock, as can be done using hypnoanesthesia, is a decided advantage in itself. And to enable the operative patient to retain his reflexes outside the anesthetic area, and thereby to prevent decubital and nerve injury, or to prevent overstretching of tendons and joints, is another great advantage. With hypnoanesthesia the patient can be given a smooth postoperative convalescence by suggesting away his wound pain so that he can breathe deeply, cough more effectively and move about his bed as though he had not been subjected to operation. How wonderful to give him peace of mind so easily and how remarkable to eliminate postoperative headache, nausea, vomiting, constipation, "gas pains" and inability to void! Feeding can be begun immediately after operation. Early ambulation can be encouraged. The discomfort of needles for fluid administration and for narcotics can be eliminated. Wounds seem to heal faster and better.

In the clinic and the cystoscopic room, much of the pain of our procedures can be alleviated and at times entirely eliminated. How much easier it is for us to catheterize, to massage prostates, to pass sounds and cystoscopes in patients who are unafraid and relaxed.[6] By raising the pain threshold in this manner patients learn from one another of the absence of pain. Fearing it less, they experience it less.

On ward rounds, pain, whether organic, functional or psychosomatic, can be alleviated or eliminated in the previously hypnotically conditioned patient in little more time than it takes to write a narcotic order. Spinal

headaches, which seem to resist the usual routine measures, respond satisfactorily to hypnotherapy. Even the pain of cancer can be relieved, and the patient can do this for himself if he is taught the technique of autohypnosis. In these persons emphasizing their faith in their religion can be very helpful.

If hypnosis can do all this, why hasn't it been used more in medicine and surgery? It is mainly because the doctor hasn't learned—because he hasn't been taught. Now that the procedure has been officially sanctioned to the profession, a few medical schools have already introduced teaching and research. The general public, through press and periodicals, has become more familiar with its intelligent purpose and usage. These factors, in time, will serve to overcome the stigma attached to hypnosis.

The chief objection to hypnoanesthesia is the extra time required to produce it. This is partly true because it requires anywhere from 10 to 30 minutes for the initial induction and, if hypnoanesthesia is planned as the sole anesthetic, at least three 15-minute conditioning sessions are required. As an adjunct to chemoanesthesia, however, after the first session, the second one can be given in the operating room, requiring a little more time but justifying this by the improved end result. Under any circumstance, the case of anesthesia induction will be enhanced by the increased rapport the anesthetist tries to establish with the patient.

From the approximate percentages previously mentioned one can see that hypnosis can be used solely for minor operations as well as in major ones in only one out of ten hypnotizable patients. When it is considered among these some would object to this method of anesthesia, still further limitation in its usage is evident.

Because of these disadvantages, hypnoanesthesia, used alone, will most likely never replace chemoanesthesia. However, if its common use as an adjunct to the latter will ever come to pass and hypnosis is to take its rightful place in medicine, graduate and postgraduate training will need to become a part of the medical school curricula. Those psychiatrists who head their departments in the medical schools can do much by initiating and then directing this teaching. The public's resentment and semisuperstitious fears can be overcome eventually if our scientific brethren will overcome their own suspicions and doubts. The great strides made in the scientific use of hypnosis to date are too strongly entrenched to relegate it again to a "dip" in the cycle.

## TECHNIQUE

The technique of hypnosis is easily mastered but, like a skilled trade, is not well learned without instruction and much practice. No one technique will be adaptable to every person, so variations will be necessary. Usually, a combination of techniques will be used. Anesthesiologists with no knowl-

edge of the technique of hypnosis can often benefit patients by giving appropriate suggestions during the twilight sleep period at the beginning and near the end of the chemoanesthesia administration. This would be applying the mechanism of the so-called "truth" drugs used as a part of one method of hypnosis.

In reviewing the literature, I have found articles on hypnoanesthesia in general surgery and in some of the subspecialties but none in urology. Therefore, for the sake of example and in order that I may document a "first" in anesthesiology in urology, I submit two case reports. In both cases hypnosis was used as the sole anesthetic and the surgery as well as the administration of anesthesia were done by the same person.

## CASE REPORTS

CASE I. This 61 year old male Negro was admitted to the Veterans Hospital on December 28, 1956, with acute retention due to a Grade IV hyperplastic prostate. A difficult catheterization was accomplished under hypnoanesthesia. Because of his ability to reach a somnambulistic stage and because, as a cardiac, he was classed as only a fair operative risk, hypnoanesthesia for a suprapubic prostatectomy was proposed and accepted.

He was conditioned on 3 alternate days, and on each occasion complete anesthesia was demonstrated with an Allis clamp. Numbness was produced from above the umbilicus to below the genitalia, and the operative procedure was described to him. A posthypnotic suggestion was given that he would go into somnambulism instantly on a finger-pointing cue.

On January 10, 1957, the morning of surgery, he was given the usual premedication consisting of 100 mg. of nembutal, 100 mg. of meperidine (Demerol) and 0.4 mg. (1/150 grain) of atropine. He was taken to the operating room alert but calm and unafraid. He responded to his cue and went into the somnambulistic hypnotic state. As a precautionary measure, a spinal catheter was introduced, and by suggestion he felt nothing in the swabbed area of his back. The blood pressure was 210/110 and the pulse 60.

After a test for anesthesia with an Allis clamp, a longitudinal midline incision was made. A wrinkling of the brow occurred but this ironed out in a few moments and the patient remained calm and made no movement during the entire operation. The recti muscles relaxed on direction and the bladder was opened transversely. A circumferential electroincision was made around the bladder neck and, with 2 fingers of the left hand in the rectum, a 100-gram prostate was enucleated and removed in 4 pieces. A No. 24 Foley catheter with 75-cc. balloon was inserted for hemostasis. A No. 22 whistletip catheter was brought through a stab as a cystostomy, the bladder closed in 2 layers, and the muscle, fascia and skin closed in the usual manner. It had been found unnecessary to use the spinal catheter during the 1½-hour operative procedure. His blood pressure rose 10 points after the skin incision was made but neither this nor the pulse of 60 showed any change throughout the operation. When awakened in the recovery room he felt fine and had no recollection of what had transpired.

During the afternoon, adjustments of the hemostatic catheter were found necessary on 2 occasions by reason of abnormal bleeding. This was done under hypnosis, and the patient had no discomfort from the manipulations. At 7 P.M. that evening

the bladder apparently filled with clots and neither catheter could be irrigated. He appeared in a cold, clammy sweat; the blood pressure dropped from 220/120 to 120/80 and his pulse rose from 60 to 90. Though he made no complaint, he seemed in a shocklike state. He was rehypnotized, using the usual cue, and taken to the cystoscopic room. His bladder was emptied of about 300 cc. of clots through a panendoscope, and an arterial spurter on the vesical neck was electrocoagulated. When returned to the recovery room and awakened, he felt and appeared much improved and had complete amnesia of the emergency treatment for his complication. The blood pressure rose to 178/98 and the pulse dropped to 72.

From then on his postoperative convalescence was smooth, though he needed several units of packed cells to bring up his hemoglobin. He was discharged 2 weeks postoperatively and when seen a month later he reported no genitourinary symptoms.

CASE II. This 68 year old Negro male was readmitted to the Veterans Hospital on July 18, 1961, to rid himself of an indwelling catheter. He had been discharged 2 months previously, after having been treated for decompensated syphilitic heart disease with aortic aneurysm and after he was found to have a neurogenic bladder along with mild prostatic obstruction due to hyperplasia. The patient manifested complete retention of 1550 cc. of urine, and several trials at voiding failed each time his indwelling catheter was removed.

Because of the neurogenic element in his bladder atony, spinal anesthesia was felt to be contraindicated, so general anesthesia for a transurethral resection of his prostate was decided upon. On August 1, 1961, following intubation under thiopental (Pentothal) sodium and shortly after the introduction of a small amount of nitrous oxide and oxygen, the patient's blood pressure dropped from 110/70 to 70/0. As this could not be corrected with rapid administration of blood, the anesthetic was discontinued and the patient was aroused after a period of artificial respiration. His operation was postponed 1 week, during which time he received another unit of blood. On the morning of the second attempt at surgery he was purposely given no premedication. After 7 cc. of 2.5 per cent thiopental sodium had been given slowly along with oxygen, his blood pressure again dropped from 140/80 to 70/30, and again the operation had to be cancelled.

The patient was anxious for his operation and accepted the concept of hypnoanesthesia as the only possible alternative. He was tested and found to be a good subject but not a somnambulist. He was given 4 preliminary hypnosis sessions, 2 of them the day prior to surgery (and 1 week following his last trip to the operating room). Posthypnotic analgesia was demonstrated to the patient by allowing him to see a needle passed through the skin of his hand. This gave an additional boost to his confidence.

The following morning an uneventful transurethral resection was done under hypnoanesthesia alone, removing 13.5 grams of tissue in a 45-minute period. During the operation the patient manifested no evidence of discomfort except when his bladder was full, at which time, as instructed, he spoke the word "full." On being awakened, while on a litter, he expressed joy and gratitude, maintaining that he had had a pleasant dream and had felt no pain. The preoperative blood pressure of 140/96 rose to around 170/120. The pulse of 118 remained stable and respirations remained around 40.

On the next morning, after a good night's sleep, the patient revealed a minimum amount of bleeding. The blood pressure was 130/86, pulse 100, and temperature 99° F. His progress was satisfactory, and he left the hospital on the eleventh postoperative day. When checked 5 weeks later he had no genitourinary symptoms and only 5 cc. of residual urine.

## SUMMARY AND CONCLUSIONS

Although the technique of hypnosis has remained essentially the same through the ages, through experience we have made some progress in the understanding of the hypnotic process handed down to us. We have traversed through cycles of rejection and acceptance of hypnotherapy, the rejection being due to charlatanic stigmata as well as to our own "astigmatism." We now find ourselves emerging from darkness into light in the rediscovery of a valuable tool in medicine. Now, through hypnosis, we can afford our patients alleviation of their fears and anxieties and give them a good preoperative night's sleep, better than that obtained with any known chemical tranquilizer. In selected cases, we can give the patient the ideal anesthetic, free of toxicity, thus reducing postoperative complications. With hypnoanalgesia we can reduce considerably the amount of anesthetic drugs needed during surgery and the amount of narcotics used afterward. Though there are limitations, and hypnoanesthesia will never displace chemoanesthesia, we have added a valuable asset to our profession, with an art so ancient and yet so new.

Two cases are cited, one a suprapubic prostatectomy and the other a transurethral resection of a prostate, both poor-risk cases, in which hypnosis was used as a sole anesthetic. The hypnoanesthesia was given and the operation was performed by one and the same person.

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Section of Urology
Veterans Administration Hospital
Coral Gables, Florida

# Index for Years 1963, 1964 and 1965

## (Volumes 43, 44 and 45)

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